

BREAKING ADVANCES

- 2403** Highlights from Recent Cancer Literature

REVIEWS

- 2405** The Role of TLR4 in Chemotherapy-Driven Metastasis
Sophia Ran
- 2411** *Ex Vivo* Culture of CTCs: An Emerging Resource to Guide Cancer Therapy
Shyamala Maheswaran and Daniel A. Haber

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2416** Early Prediction of Disease Progression in Small Cell Lung Cancer: Toward Model-Based Personalized Medicine in Oncology
Núria Buil-Bruna, Tarjinder Sahota, José-María López-Picazo, Marta Moreno-Jiménez, Salvador Martín-Algarra, Benjamin Ribba, and Iñaki F. Trocóniz

Précis: The proposed statistical framework can be used to aid personalization of disease monitoring in oncology.

- 2426** Cell–Cell Adhesion and Cytoskeleton Tension Oppose Each Other in Regulating Tumor Cell Aggregation

Laure Saias, Aurélie Gomes, Martine Cazales, Bernard Ducommun, and Valérie Lobjois

Précis: These findings reveal new principles that govern multicellular aggregation, possibly paving the way for new therapeutic opportunities.

MICROENVIRONMENT AND IMMUNOLOGY

- 2434** IL13 Receptor $\alpha 2$ Signaling Requires a Scaffold Protein, FAM120A, to Activate the FAK and PI3K Pathways in Colon Cancer Metastasis

Rubén A. Bartolomé, Irene García-Palmero, Sofía Torres, María López-Lucendo, Irina V. Balyasnikova, and J. Ignacio Casal

Précis: This study identifies a scaffold protein required for downstream signaling of the IL13 receptor, which regulates invasion and metastasis in colon cancer, with potential implications for therapy in this setting.

- 2445** Endothelial ALK1 Is a Therapeutic Target to Block Metastatic Dissemination of Breast Cancer



Sara I. Cunha, Matteo Bocci, John Lötvrot, Nikolas Eleftheriou, Pernilla Roswall, Eugenia Cordero, Linda Lindström, Michael Bartoschek, B. Kristian Haller, R. Scott Pearsall, Aaron W. Mulivor, Ravindra Kumar, Christer Larsson, Jonas Bergh, and Kristian Pietras

Précis: These findings offer preclinical proof of concept for the utility of ALK1 inhibitors to treat metastatic breast cancer, with immediate implications for evaluation of this strategy in the clinic.

PREVENTION AND EPIDEMIOLOGY

- 2457** Novel Associations between Common Breast Cancer Susceptibility Variants and Risk-Predicting Mammographic Density Measures

Jennifer Stone, Deborah J. Thompson, Isabel dos-Santos-Silva, Christopher Scott, Rulla M. Tamimi, Sara Lindstrom, Peter Kraft, Aditi Hazra, Jingmei Li, Louise Eriksson, Kamila Czene, Per Hall, Matt Jensen, Julie Cunningham, Janet E. Olson, Kristen Purrington, Fergus J. Couch, Judith Brown, Jean Leyland, Ruth M.L. Warren, Robert N. Luben, Kay-Tee Khaw, Paula Smith, Nicholas J. Wareham, Sebastian M. Jud, Katharina Heusinger, Matthias W. Beckmann, Julie A. Douglas, Kanaan P. Shah, Heang-Ping Chan, Mark A. Helvie, Loic Le Marchand, Laurence N. Kolonel, Christy Woolcott, Gertraud Maskarinec, Christopher Haiman, Graham G. Giles, Laura Baglietto, Kavitha Krishnan, Melissa C. Southey, Carmel Apicella, Irene L. Andrusis, Julia A. Knight, Giske Ursin, Grethe I. Grenaker Alnaes, Vessela N. Kristensen, Anne-Lise Borresen-Dale, Inger Torhild Gram, Manjeet K. Bolla, Qin Wang, Kyriaki Michailidou, Joe Dennis, Jacques Simard, Paul Pharoah, Alison M. Dunning, Douglas F. Easton, Peter A. Fasching, V. Shane Pankratz, John L. Hopper, and Celine M. Vachon

Précis: These findings deepen the evidence of shared genetic determinants between breast cancer risk and mammographic density measures, strengthening the likelihood of common etiologic pathways.

- 2468** NHANES 2009–2012 Findings: Association of Sexual Behaviors with Higher Prevalence of Oral Oncogenic Human Papillomavirus Infections in U.S. Men

Anil K. Chaturvedi, Barry I. Graubard, Tatevik Broutian, Robert K.L. Pickard, Zhen-yue Tong, Weihong Xiao, Lisa Kahle, and Maura L. Gillison

Précis: These epidemiologic results indicate that the incidence of HPV-positive oropharyngeal cancer is higher and rising more sharply among men than women in the United States because of gender-associated sexual behaviors.

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THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 2478** Targeting Mitochondria with Avocatin B Induces Selective Leukemia Cell Death
Eric A. Lee, Leonard Angka, Sarah-Grace Rota, Thomas Hanlon, Andrew Mitchell, Rose Hurren, Xiao Ming Wang, Marcela Gronda, Ezel Boyaci, Barbara Bojko, Mark Minden, Shrivani Sriskanthadevan, Alessandro Datti, Jeffery L. Wrana, Andrea Edginton, Janusz Pawliszyn, Jamie W. Joseph, Joe Quadrilatero, Aaron D. Schimmer, and Paul A. Spagnuolo

Précis: A natural product derived from avocado fruit can selectively eradicate leukemia cells based on a specific difference in mitochondrial function.

- 2489** Acquired Resistance to the Mutant-Selective EGFR Inhibitor AZD9291 Is Associated with Increased Dependence on RAS Signaling in Preclinical Models



Catherine A. Eberlein, Daniel Stetson, Aleksandra A. Markovets, Katherine J. Al-Kadhimi, Zhongwu Lai, Paul R. Fisher, Catherine B. Meador, Paula Spitzler, Eiki Ichihara, Sarah J. Ross, Miika J. Ahdesmaki, Ambar Ahmed, Laura E. Ratcliffe, Elizabeth L. Christey O'Brien, Claire H. Barnes, Henry Brown, Paul D. Smith, Jonathan R. Dry, Garry Beran, Kenneth S. Thress, Brian Dougherty, William Pao, and Darren A.E. Cross

Précis: These results offer early insight into how acquired resistance arises to a new mutation-selective inhibitor of EGFR that is in fast-track clinical development, illustrating the inescapable cat-and-mouse chase in the evolution of cancer cell-targeting drugs in the management of cancer patients.

- 2501** Breast Cancer Detection by B7-H3-Targeted Ultrasound Molecular Imaging

Sunitha V. Bachawal, Kristin C. Jensen, Katherine E. Wilson, Lu Tian, Amelie M. Lutz, and Jürgen K. Willmann

Précis: The immunoregulator B7-H3 is differentially expressed on vascular endothelial cells of breast cancer compared with normal or benign breast pathologies, and this study offers a preclinical proof of concept for the use of B7-H3-targeted ultrasound molecular imaging to improve the diagnostic accuracy of breast cancer detection in patients.

- 2510** Effects of Sorafenib Dose on Acquired Reversible Resistance and Toxicity in Hepatocellular Carcinoma

Elizabeth A. Kuczynski, Christina R. Lee, Shan Man, Eric Chen, and Robert S. Kerbel

Précis: Reductions in the plasma levels of the tyrosine kinase inhibitor sorafenib that occur naturally in some patients represent a potential contributing cause of drug resistance, with broader implications for optimal dosing of other tyrosine kinase inhibitors.

- 2520** Grapefruit-Derived Nanovectors Use an Activated Leukocyte Trafficking Pathway to Deliver Therapeutic Agents to Inflammatory Tumor Sites

Qilong Wang, Yi Ren, Jingyao Mu, Nejat K. Egilmez, Xiaoyin Zhuang, Zhongbin Deng, Lifeng Zhang, Jun Yan, Donald Miller, and Huang-Ge Zhang

Précis: This interesting report defines and characterizes the tumor-targeting features of a readily available, generalizable, and nontoxic vehicle to improve the targeted delivery of therapeutic drugs to cancerous or precancerous sites, possibly offering a low-cost clinical formulation strategy to widen the therapeutic window for many drugs.

- 2530** Drug Redeployment to Kill Leukemia and Lymphoma Cells by Disrupting SCD1-Mediated Synthesis of Monounsaturated Fatty Acids



Andrew D. Southam, Farhat L. Khanim, Rachel E. Hayden, Julia K. Constantinou, Katarzyna M. Koczula, Robert H. Michell, Mark R. Viant, Mark T. Drayson, and Chris M. Bunce

Précis: The combination of two drugs found to have anticancer activity in patients is mechanistically linked in this study to decreased levels of a candidate therapeutic target involved in fatty-acid synthesis.

TUMOR AND STEM CELL BIOLOGY

- 2541** Grade-Dependent Metabolic Reprogramming in Kidney Cancer Revealed by Combined Proteomics and Metabolomics Analysis

Hiromi I. Wettersten, A. Ari Hakimi, Dexter Morin, Cristina Bianchi, Megan E. Johnstone, Dallas R. Donohoe, Josephine F. Trott, Omran Abu Aboud, Steven Stirdivant, Bruce Neri, Robert Wolfert, Benjamin Stewart, Roberto Perego, James J. Hsieh, and Robert H. Weiss

Précis: This work uncovers new aspects of grade-dependent metabolic reprogramming in renal cancers that could lead to novel personalized treatments, including the use of inhibitors of glucose, glutamine, and tryptophan metabolism that are being developed in other clinical settings.

- 2553** Lin28B/Let-7 Regulates Expression of Oct4 and Sox2 and Reprograms Oral Squamous Cell Carcinoma Cells to a Stem-like State



Chian-Shiu Chien, Mong-Lien Wang, Pen-Yuan Chu, Yuh-Lih Chang, Wei-Hsiu Liu, Cheng-Chia Yu, Yuan-Tzu Lan, Pin-I. Huang, Yi-Yen Lee, Yi-Wei Chen, Wen-Liang Lo, and Shih-Hwa Chiou

Précis: These results show how cancer stem-like properties are controlled in oral squamous cancers, and how this control system may promote drug resistance and tumor relapse in advanced cancers.

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- 2566** G-CSF Promotes Neuroblastoma Tumorigenicity and Metastasis via STAT3-Dependent Cancer Stem Cell Activation
Saurabh Agarwal, Anna Lakoma, Zaowen Chen, John Hicks, Leonid S. Metelitsa, Eugene S. Kim, and Jason M. Shohet

Précis: This seminal study challenges the clinical use of G-CSF as a treatment to support white blood cell counts in children with neuroblastoma, based on the ability of this factor to promote the growth of the cancer stem-like cell population in this setting.

CORRECTIONS

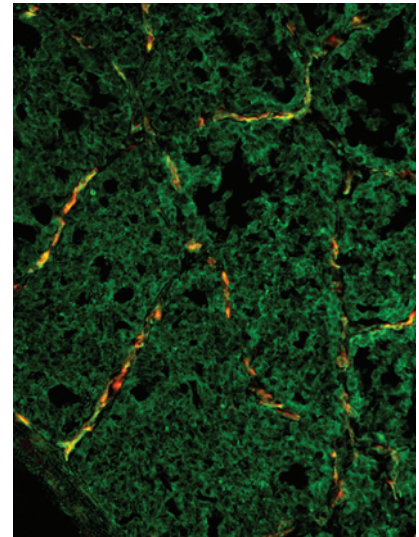
- 2580** Correction: Identification of Pax5 as a Target of MTA1 in B-cell Lymphomas
- 2582** Correction: Metastasis-Associated Protein 1 Transgenic Mice: A New Model of Spontaneous B-cell Lymphomas

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ABOUT THE COVER

Ultrasound is a complementary imaging modality for detection of mammographically occult breast cancers, especially in patients with dense breast tissue. Diagnostic accuracy of ultrasound in these patients can be significantly improved using contrast agents targeted at molecular signatures on the tumor neovasculature. In a large scale immunohistochemical staining analysis of human tissues, it was found that B7-H3 is differentially expressed in breast cancer-associated vascular endothelial cells compared with normal, benign, and precursor lesions. Also, B7-H3-targeted ultrasound molecular imaging allowed detection of breast cancer in a transgenic mouse model of breast cancer development. For details, see article by Bachawal and colleagues on page 2501.



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