Endothelial ALK1 Is a Therapeutic Target to Block Metastatic Dissemination of Breast Cancer
Sara I. Cunha, Matteo Bocci, John Lövrot, Nikolas Eleftheriou, Pernilla Roswall, Eugenia Cordero, Linda Lindström, Michael Bartoschek, B. Kristian Haller, R. Scott Peairs, Aaron W. Mulivor, Ravinda Kumar, Christra 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.

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

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.


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 Gronde, Ezel Boyaci, Barbara Bojko, Mark Minden, Shirvani Sriskanthadevan, Alessandro Datti, Jeffery L. Wran, Andrea Edginton, Janusz Pawlisy, Jamie W. Joseph, Joe Quadrilateralero, 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  
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  
Elizabith 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. Kochu, Robert H. Mitchell, 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, Dester Morin, Cristina Bianchi, Megan E. Johnstone, Dallas R. Donohoe, Josephine F. Trot, Omran Abu Aboud, Steven Stürdivant, Bruce Neri, Robert Wölfert, Benjamin Stewart, Roberto Peregio, 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  
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.
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.

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

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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