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PRIORITY REPORT

4676 Kinase Domain Activation of FGFR2 Yields High-Grade Lung Adenocarcinoma Sensitive to a Pan-FGFR Inhibitor in a Mouse Model of NSCLC

Precis: In developing a unique mouse model of lung adenocarcinoma, this study may improve what have been limited opportunities for preclinical drug discovery and development in this setting.
INTEGRATED SYSTEMS AND TECHNOLOGIES

4685 Polarization-Sensitive Multimodal Imaging for Detecting Breast Cancer
Rakesh Patel, Ashraf Khan, Robert Quinlan, and Anna N. Yaroslavsky
Précis: This study describes a novel noninvasive imaging method that allows for rapid and accurate intraoperative detection of breast cancer margins.

4694 A Search for Novel Cancer/Testis Antigens in Lung Cancer Identifies VCX/Y Genes, Expanding the Repertoire of Potential Immunotherapeutic Targets
Ayumu Taguchi, Allen D. Taylor, Jaime Rodriguez, Muge Celiktas, Hui Liu, Xiaoqin Han, Prathibha Ranganathan, Xiaoxia Zhu, Thiago DaSilva, Wei Liu, Francesca Ratti, Renee M. Demarest, Cristos Tzimas, Meghan Rice, Rodrigo Vasquez-Del Carpio, Nadia Dahanane, David J. Robbins, and Anthony J. Capobianco
Précis: These results offer preclinical proof-of-concept for an Hsp70 regulatory complex as an appealing anticancer target for the generalized treatment of human malignancy.

MICROENVIRONMENT AND IMMUNOLOGY

4706 Osteopontin Shapes Immunosuppression in the Metastatic Niche
Sabina Sangaletti, Claudio Tripodo, Sara Sandri, Ilaria Torselli, Caterina Vitali, Chiara Ratti, Laura Botti, Alessia Burocchi, Rossana Porcasi, Andrea Tomirotti, Mario P. Colombo, and Claudia Chiodoni
Précis: Activities of a prometastatic molecule appear to differ to some extent when produced by tumor cells versus host immune cells however, from either source it helps establish local immunosuppression within metastatic sites.

4720 IL-1β-Mediated Repression of microRNA-101 Is Crucial for Inflammation-Promoted Lung Tumorigenesis
Lin Wang, Ling-Fei Zhang, Jing Wu, Shu-Jun Xu, Yang-Yang Xu, Dangsheng Li, Jia-Tao Lou, and Mo-Fang Liu
Précis: microRNA-101 provides a molecular connection between pathogenic inflammation and lung tumorigenesis by regulating Lin28B, an oncogenic RNA-binding protein with pleiotropic roles in cancer including stem-like cell function.

MOLECULAR ANDcellular PATHOBIOLOGY

4731 Hsp70–Bag3 Interactions Regulate Cancer-Related Signaling Networks
Précis: This study confirms the suspicion that prospects for effective immunotherapy are far more likely to emerge from targeting multiple tumor antigens than single tumor antigens.

4741 NACK Is an Integral Component of the Notch Transcriptional Activation Complex and Is Critical for Development and Tumorigenesis
Kelly L. Weaver, Marie-Cottilde Alves-Guerra, Ke Jin, Zhiqiang Wang, Xiaoning Han, Prathibha Ranganathan, Xiaoxia Zhu, Thiago DaSilva, Wei Liu, Francesca Ratti, Renee M. Demarest, Cristos Tzimas, Meghan Rice, Rodrigo Vasquez-Del Carpio, Nadia Dahanane, David J. Robbins, and Anthony J. Capobianco
Précis: This study illuminates a novel critical part of the Notch receptor signaling pathway, which has emerged as an important driver of a variety of aggressive human cancers.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4752 Antitumor Effects in Hepatocarcinoma of Isoform-Selective Inhibition of HDAC2
Yun-Han Lee, Daekwan Seo, Kyung-Ju Choi, Jesper B. Andersen, Min-Ah Won, Mitsuteru Kitade, Luis E. Gómez-Quiroz, Adam D. Judge, Jens U. Marquardt, Chiara Raggi, Elizabeth A. Conner, Ian MacLachlan, Valentina M. Factor, and Snorri S. Thorgeirsson
Précis: Systemic inactivation of a disease-specific HDAC isoform can achieve therapeutic efficacy, as shown by this preclinical proof-of-concept study for treatment of liver cancer.

4762 Combined SFK/mTOR Inhibition Prevents Rapamycin-Induced Feedback Activation of AKT and Elicits Efficient Tumor Regression
Jennifer L. Yori, Kristen L. Lozada, Darcie D. Seachrist, Jonathan D. Mosley, Fadi W. Abdul-Karim, Christine N. Booth, Chris A. Flask, and Ruth A. Keri
Précis: Results from this combination therapy study may help improve the mainly inefficacious effects of mTOR inhibitors in clinical trials, addressing the weaknesses of an erstwhile general approach to cancer cell eradication.
Immediate Utility of Two Approved Agents to Target Both the Metabolic Mevalonate Pathway and Its Restorative Feedback Loop
Aleksandra Pandyra, Peter J. Mullen, Manpreet Kalkat, Rosemary Yu, Janice T. Pong, Zhihua Li, Suzanne Trudel, Karl S. Lang, Mark D. Minden, Aaron D. Schimmer, and Linda Z. Penn
Précis: This article provides an excellent illustration of polypharmacology discovery by tapping the existing armamentarium of approved drugs to identify immediately tractable new experimental therapies for clinical evaluation.

AMPK Reverses the Mesenchymal Phenotype of Cancer Cells by Targeting the Akt–MDM2–Foxo3a Signaling Axis
Chih-Chien Chou, Kuen-Haur Lee, I-Lu Lai, Dasheng Wang, Xiaokui Mo, Samuel K. Kulp, Charles L. Shapiro, and Ching-Shih Chen
Précis: This work illuminates a mechanism of EMT limitation in cancer cells, along with preclinical support for a tractable therapeutic strategy to reverse mesenchymal phenotypes associated with invasion and metastasis.

Neuronal Pentraxin 2 Supports Clear Cell Renal Cell Carcinoma by Activating the AMPA-Selective Glutamate Receptor-4
Christina A. von Roemeling, Derek C. Radisky, Laura A. Marlow, Simon J. Cooper, Stefan K. Grebe, Panagiotis Z. Anastasiadis, Han W. Tun, and John A. Copland
Précis: A secreted protein exclusively studied in the context of neuronal cell function appears to act through a calcium signaling pathway to support the pathogenicity of deadly kidney cancers, with immediate implications for a possible clinical treatment strategy.

Pyrvinium Attenuates Hedgehog Signaling Downstream of Smoothened
Bin Li, Dennis Liang Pei, Colin A. Flaveny, Nadia Dahmane, Valerie Baubet, Zhiqiang Wang, Feng Bai, Xin-Hai Pei, Jezabel Rodriguez-Blanco, Brian Hang, Darren Orton, Lu Han, Baolin Wang, Anthony J. Capobianco, Ethan Lee, and David J. Robbins
Précis: An FDA-approved pinworm drug with potent activity as a casein kinase-Iα agonist is found to robustly inhibit Hedgehog signaling in tumors, including those resistant to existing Hedgehog pathway inhibitors, with immediate implications for clinical testing.

Definition of PKC-α, CDK6, and MET as Therapeutic Targets in Triple-Negative Breast Cancer
Yi-Hsin Hsu, Jun Yao, Li-Chuan Chan, Ting-Jung Wu, Jennifer L. Hsu, Yueh-Fu Fang, Yongkun Wei, Yun Wu, Wen-Chien Huang, Chien-Liang Liu, Yuan-Ching Chang, Ming-Yang Wang, Chia-Wei Li, Jia Shen, Mei-Kuang Chen, Aysegul A. Sahin, Anil Sood, Gordon B. Mills, Dihua Yu, Gabriel N. Hortobagyi, and Mien-Chie Hung
Précis: These findings define three kinases critical for growth of an aggressive subtype of breast cancer, offering a preclinical rationale to target their activity as an effective therapy.
Epigenetic States of Cells of Origin and Tumor Evolution Drive Tumor-Initiating Cell Phenotype and Tumor Heterogeneity
Kin-Hoe Chow, Dong-Mi Shin, Molly H. Jenkins, Emily E. Miller, David J. Shih, Seungbum Choi, Benjamin E. Low, Vivek Philip, Brad Rybinski, Roderick T. Bronson, Michael D. Taylor, and Kyuson Yun

Précis: This study probes the sources of tumor heterogeneity, a core research challenge that—despite its recognition by clinical pathologists for many years and its recent rediscovery by molecular geneticists—still represents the chief weakness of all cancer cell-targeted therapeutic strategies.

TRIM29 Suppresses TWIST1 and Invasive Breast Cancer Behavior

Précis: TRIM29 exerts complex roles in cancer, but in breast cancer it appears to function as a tumor suppressor by suppressing a core regulator of the epithelial–mesenchymal transition, a pivotal step in driving invasive and metastatic behavior.

TRIB1 Supports Prostate Tumorigenesis and Tumor-Propagating Cell Survival by Regulation of Endoplasmic Reticulum Chaperone Expression
Tetsuo Mashima, Taeko Soma-Nagae, Toshiro Migita, Ryoko Kinoshita, Atsushi Iwamoto, Takeshi Yuasa, Junji Yonese, Yuichi Ishikawa, and Hiroyuki Seimiya

Précis: Prostate cancer stem-like cells appear to be addicted to oncogenic signals from an endoplasmic reticulum-dependent stress response pathway, a finding with potential therapeutic implications.

IDH1 R132H Mutation Generates a Distinct Phospholipid Metabolite Profile in Glioma
Morteza Esmaeili, Bob C. Hamans, Anna C. Navis, Remco van Horssen, Tone F. Bathe, Ingrid S. Gribbestad, William P. Leenders, and Arend Heerschap

Précis: This study reports novel noninvasive biomarkers of IDH-mutant gliomas that may help to guide treatments to target aberrant metabolism in these aggressive brain tumors.

II15RA Drives Antagonistic Mechanisms of Cancer Development and Immune Control in Lymphocyte-Enriched Triple-Negative Breast Cancers
Pierfrancesco Marra, Sumi Mathew, Anita Grigoriadis, Yin Wu, Fernanda Kyle-Cezar, Johnathan Watkins, Mamunur Rashid, Emanuele De Rinaldis, Sonya Hessey, Patrycja Gazinska, Adrian Hayday, and Andrew Tutt

Précis: Expression of an immune memory-inducing receptor in some triple-negative breast cancers, usually only expressed by T cells, may offer a mechanistic explanation for the paradoxical association of some of these high-grade tumors with better survival outcomes.

Epigenetic Targeting of Ovarian Cancer Stem Cells
Yinu Wang, Horacio Cardenas, Fang Fang, Salvatore Condello, Pietro Taverna, Matthew Segar, Yunlong Liu, Kenneth P. Nephew, and Daniela Matei

Précis: These results suggest that epigenome-targeting strategies can reprogram residual cancer stem-like cells to a differentiated state, thereby helping prevent the development of recurrent, chemoresistant disease.

Live-Cell Imaging of Invasion and Intravasation in an Artificial Microvessel Platform
Andrew D. Wong and Peter C. Searson

Précis: An artificial microvessel platform can be used to obtain striking images and mechanistic insights into how cancer cells invade the local microenvironment and enter and exit vessels, providing a new tool to help unravel the complexities of metastasis and its prevention and treatment.

LETTERS TO THE EDITOR

A Synthetic Lethality-Based Strategy to Treat Cancers Harboring a Genetic Deficiency in the Chromatin Remodeling Factor BRG1—Letter
Kenneth W. Thompson, Stefanie B. Marquez, and David Reisman

Proposal for a Synthetic Lethality Therapy Using the Paralog Dependence of Cancer Cells—Response
Takahiro Oike, Hideaki Ogihara, Takashi Nakano, and Takashi Kohno
CORRECTIONS

Correction: The TGFβ–miR200–Mig6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors

Correction: Chk2 Phosphorylation of Survivin-ΔEx3 Contributes to a DNA Damage-Sensing Checkpoint in Cancer

ABOUT THE COVER

Confocal microscopy analysis for osteopontin performed on myeloid-derived suppressor cells (MDSC) shows osteopontin (red) localized under the cellular membrane but not colocalized with the ER marker concanavalin A (green) in MDSC. This picture is suggestive of the existence of an intracellular form, rather than a secreted form of osteopontin, in MDSC. For details, see article by S. Sangaletti and colleagues on page 4706.