Suppression of Feedback Loops Mediated by PI3K/mTOR Induces Multiple Overactivation of Compensatory Pathways: An Unintended Consequence Leading to Drug Resistance

Enrique Rozengurt, Heloisa P. Soares, and James Sinnet-Smith

Delineating the mTOR Kinase Pathway Using a Dual TORC1/2 Inhibitor, AZD8055, in Multiple Myeloma

Diana Cirstea, Loredana Santo, Teru Hideshima, Homare Eda, Yuko Mishima, Neeharika Nemani, Anuj Mahindrka, Andrew Yee, Gullu Gorgun, Yiguo Hu, Hiroto Ohguchi, Rikio Suzuki, Francesca Cottini, Sylvie M. Guichard, Kenneth C. Anderson, and Noopur Raje

Dual Targeting of Hypoxia and Homologous Recombination Repair Dysfunction in Triple-Negative Breast Cancer

Francis W. Hunter, Huai-Ling Hsu, Jiechuang Su, Susan M. Pullen, William R. Wilson, and Jingli Wang

Novel Selective Estrogen Mimics for the Treatment of Tamoxifen-Resistant Breast Cancer

Mary Ellen Molloy, Bethany E. Perez White, Teshome Gherezghiher, Bradley T. Michalsen, Rui Xiong, Hitisha Patel, Huiping Zhao, Philipp Y. Maximov, V. Craig Jordan, Gregory R.J. Thatcher, and Debra A. Tonetti

Pazopanib, a Novel Multitargeted Kinase Inhibitor, Shows Potent In Vitro Antitumor Activity in Gastric Cancer Cell Lines with FGFR2 Amplification

Seung Tae Kim, Hye-Lim Jang, Su Jin Lee, Jeeyun Lee, Yoon-La Choi, Kyoungh-Mee Kim, Jeonghee Cho, Se Hoon Park, Young Suk Park, Ho Yeong Lim, Masakazu Yashiro, Won Ki Kang, and Joon Oh Park

Small Molecule BMH-Compounds That Inhibit RNA Polymerase I and Cause Nucleolar Stress

Karita Pettonen, Laureen Colis, Hester Liu, Sari Jaama, Zhewei Zhang, Taija af Hallstrom, Henna M. Moore, Paul Strajuddin, and Marikki Laiho

Monensin Inhibits Epidermal Growth Factor Receptor Trafficking and Activation: Synergistic Cytotoxicity in Combination with EGFR Inhibitors

Khalil Dayekh, Stephanie Johnson-Obaseki, Martin Corsten, Patrick J. Villeneuve, Harmanjotinder S. Sekhon, Johanne I. Weberpals, and Jim Dimitroulakos

Targeted Silencing of MLL5 Inhibits Tumor Growth and Promotes Gamma-Irradiation Sensitization in HPV16/18-Associated Cervical Cancers

Dawn Sijin Nin, Chow Wenn Yew, Sun Kuie Tay, and Lih-Wen Deng

Bisphosphonates Inhibit Stellate Cell Activity and Enhance Antitumor Effects of Nanoparticle Albumin–Bound Paclitaxel in Pancreatic Ductal Adenocarcinoma


Development of Targeted Near-Infrared Imaging Agents for Prostate Cancer

Xinning Wang, Steve S. Huang, Warren D.W. Heston, Hong Guo, Bing-Cheng Wang, and James P. Basilion
## Table of Contents

### LARGE MOLECULE THERAPEUTICS

2607  **Anti-MET ImmunoPET for Non–Small Cell Lung Cancer Using Novel Fully Human Antibody Fragments**
       Keyu Li, Richard Tavarez, Kirstin A. Zettlitz, Shannon M. Mumenthaler, Parag Mallick, Yu Zhou, James D. Marks, and Anna M. Wu

2618  **Preclinical Profile of the HER2-Targeting ADC SYD983/SYD985: Introduction of a New Duocarmycin-Based Linker-Drug Platform**
       Wim Dokter, Ruud Ubink, Miranda van der Lee, Monique van der Vleuten, Tanja van Achterberg, Danielle Jacobs, Eline Loosveld, Diels van den Dobbelsteen, David Egging, Ellen Mattaan, Patrick Groothuis, Patrick Beusker, Ruud Coumans, Ronald Elgersma, Wiro Menge, John Joosten, Henri Spijker, Tijl Huijbregts, Vincent de Groot, Michel Eppink, Guy de Roo, Gijs Verheijden, and Marco Timmers

2630  **An Antimesothelin-Monomethyl Auristatin E Conjugate with Potent Antitumor Activity in Ovarian, Pancreatic, and Mesothelioma Models**

2641  **A Chemically Defined Trifunctional Antibody–Cytokine–Drug Conjugate with Potent Antitumor Activity**
       Thomas List, Giulio Casi, and Dario Neri

2653  **Efficacy of RG7787, a Next-Generation Mesothelin-Targeted Immunotoxin, against Triple-Negative Breast and Gastric Cancers**
       Christine Alewine, Laiman Xiang, Takao Yamori, Gerhard Niederfellner, Klaus Bosslet, and Ira Pastan

2662  **MEDI-573, Alone or in Combination with Mammalian Target of Rapamycin Inhibitors, Targets the Insulin-like Growth Factor Pathway in Sarcomas**
       Haihong Zhong, Christine Fazenbaker, Shannon Breen, Cui Chen, Jiaqi Huang, Christopher Morehouse, Yihong Yao, and Robert E. Hollingsworth

2674  **Therapeutic Targeting of Angiogenesis with a Recombinant CTT Peptide–Endostatin Mimic–Kringle 5 Protein**
       Houbin Wang, Zhigang Yang, and Jun Gu

2688  **Development of Human Serine Protease-Based Therapeutics Targeting Fn14 and Identification of Fn14 as a New Target Overexpressed in TNBC**
       Hong Zhou, Khalid A. Mohamedali, Ana Maria Gonzalez-Angulo, Yu Cao, Mary Migliorini, Lawrence H. Cheung, Janine LoBello, Xiudong Lei, Yuan Qi, Walter N. Hittelman, Jeffrey A. Winkles, Nhan L. Tran, and Michael G. Rosenblum

### CANCER BIOLOGY AND SIGNAL TRANSDUCTION

2706  **Longitudinal Time-Dependent Effects of Irradiation on Multidrug Resistance in a Non–Small Lung Cancer Cell Line**
       Yumiko Kono, Keita Utsunomiya, Shouhei Kanno, and Noboru Tanigawa

2713  **SNAI2 Modulates Colorectal Cancer 5-Fluorouracil Sensitivity through miR145 Repression**
       Victoria J. Findlay, Cindy Wang, Lourdes M. Nogueira, Katie Hurst, Daniel Quirk, Stephen P. Ethier, Kevin F. Staveley O’Carroll, Dennis K. Watson, and E. Ramsay Camp

2727  **Tissue Penetration and Activity of Camptothecins in Solid Tumor Xenografts**
       Alastair H. Kyle, Jennifer H.E. Baker, Maria-Jose Gandolfo, Stefan A. Reinsberg, and Andrew I. Minchinton

### COMPANION DIAGNOSTICS AND CANCER BIOMARKERS

2738  **A Comprehensive Evaluation of Biomarkers Predictive of Response to PI3K Inhibitors and of Resistance Mechanisms in Head and Neck Squamous Cell Carcinoma**
       Tuhina Mazumdar, Lauren A. Byers, Patrick Kwok, Shing Ng, Gordon B. Mills, Shaohua Peng, Lixia Diao, You-Hong Fan, Katherine Stemke-Hale, John V. Heymach, Jeffrey N. Myers, Bonnie S. Glisson, and Faye M. Johnson
MODELS AND TECHNOLOGIES

Identification of Kinase Inhibitor Targets in the Lung Cancer Microenvironment by Chemical and Phosphoproteomics  
Manuela Gridling, Scott B. Ficarro, Florian P. Breitwieser, Lanxi Song, Katja Parapatics, Jacques Colinge, Eric B. Haura, Jarrod A. Marto, Giulio Superti-Furga, Keiryn L. Bennett, and Uwe Rix

LETTERS TO THE EDITOR

PDT with a Glucose-Conjugated Chlorin for GIST—Letter  
Mark Linch and Andrew J. Hayes

PDT with a Glucose-Conjugated Chlorin for GIST—Response  
Hiromi Kataoka and Mamoru Tanaka

CORRECTION

Correction: The Aurora Kinase A Inhibitor MLN8237 Enhances Cisplatin-Induced Cell Death in Esophageal Adenocarcinoma Cells

ABOUT THE COVER

Interrelation between vasculature, blood flow, proliferation, and hypoxia is shown in an HCT116 tumor xenograft 24 hours following irinotecan treatment. Irinotecan initially halts proliferation throughout the tissue but by 24 hours the S-phase fraction returns to near-control levels. The image was produced using multiplexed immunohistochemistry to illustrate the effects of drugs in the context of the tumor microenvironment. Greyscale images of the individual staining patterns were coregistered to produce the composite image shown here. HCT116 xenografts exhibit a corded architecture, where sheaths of tumor cells can be seen to surround individual vessels. Cells can survive to ~150 m away from the blood vessels but become increasingly oxygen-deprived and eventually necrose. For details, see the article by Kyle and colleagues on page 2727.