### Table of Contents

#### Highlights of This Issue 2475

**REVIEW**

**2477** 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

**SMALL MOLECULE THERAPEUTICS**

**2489** 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 Nemanii, Anuj Mahindra, Andrew Yee, Gullu Gorgun, Yiguo Hu, Hiroto Ohguchi, Rikio Suzuki, Francesca Cottini, Sylvie M. Guichard, Kenneth C. Anderson, and Noopur Raje

**2501** 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

**2515** 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

**2527** 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

**2537** Small Molecule BMH-Compounds That Inhibit RNA Polymerase I and Cause Nucleolar Stress

Karita Peltonen, Laureen Colis, Hester Liu, Sari Jaamaa, Zhiwei Zhang, Taija af Hallstrom, Henna M. Moore, Paul Strajuddin, and Marikki Laiho

**2547** The Fibroblast Growth Factor Receptor Genetic Status as a Potential Predictor of the Sensitivity to CH5183284/Debio 1347, a Novel Selective FGFR Inhibitor

Yoshito Nakanishi, Nukinori Akiyama, Toshiyuki Tsukaguchi, Toshihiko Fujii, Kiyowi Sakata, Hitoshi Sase, Takehito Isobe, Kenji Morikami, Hidetoshi Shindo, Toshiyuki Mio, Hirotsuo Ebitake, Naoki Taka, Yuko Araki, and Nobuya Ishii

**2559** 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 L. Websterpals, and Jim Dimitroulakos

**2572** Targeted Silencing of MLL5 Inhibits Tumor Growth and Promotes Gamma-Irradiation Sensitization in HPV16/18-Associated Cervical Cancers

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

**2583** Bisphosphonates Inhibit Stellate Cell Activity and Enhance Antitumor Effects of Nanoparticle Albumin–Bound Paclitaxel in Pancreatic Ductal Adenocarcinoma


**2595** 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
LARGE MOLECULE THERAPEUTICS

2607 Anti-MET ImmunoPET for Non–Small Cell Lung Cancer Using Novel Fully Human Antibody Fragments
Keyu Li, Richard Tavare, 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 Mattaart, Patrick Groothuis, Patrick Beusker, Ruud Coumans, Ronald Elgersma, Wijs Menge, John Joosten, Henri Spijkers, 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

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, Shohei 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

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 Collinge, 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.