## THERAPEUTIC DISCOVERY

### Highlights of This Issue 2075

#### 2077 Evaluating the Therapeutic Potential of a Non-Natural Nucleotide That Inhibits Human Ribonucleotide Reductase
Md. Faiz Ahmad, Qun Wan, Shalini Jha, Edward Motea, Anthony Berdis, and Chris Dealwis

#### 2087 Targeting TRAIL Death Receptor 4 with Trivalent DR4 Atrimer Complexes

#### 2096 A New Nonestrogenic Steroidal Inhibitor of 17β-Hydroxysteroid Dehydrogenase Type I Blocks the Estrogen-Dependent Breast Cancer Tumor Growth Induced by Estrone
Diana Ayan, René Maltais, Jenny Roy, and Donald Poirier

#### 2105 Reexpression of Tumor Suppressor, sFRP1, Leads to Antitumor Synergy of Combined HDAC and Methyltransferase Inhibitors in Chemoresistant Cancers
Simon J. Cooper, Christina A. von Roemeling, Kylie H. Kang, Laura A. Marlow, Stefan K. Grebe, Michael E. Menefee, Han W. Tun, Gerardo Colon-Otero, Edith A. Perez, and John A. Copland

#### 2116 The Inhibitor of Histone Deacetylases Sodium Butyrate Enhances the Cytotoxicity of Mitomycin C
Anastas Gospodinov, Stanislava Popova, Ivelina Vassileva, and Boyka Anachkova

#### 2127 Cell Intrinsic Role of COX-2 in Pancreatic Cancer Development
Reginald Hill, Yunfeng Li, Linh M. Tran, Sarah Dry, Joseph Hargan Calvopina, Alejandro Garcia, Christine Kim, Ying Wang, Timothy R. Donahue, Harvey R. Herschman, and Hong Wu

#### 2138 Cdk4/6 Inhibition Induces Epithelial–Mesenchymal Transition and Enhances Invasiveness in Pancreatic Cancer Cells
Fang Liu and Murray Korc

### PRECLINICAL DEVELOPMENT

#### 2149 Combined Therapy with Mutant-Selective EGFR Inhibitor and Met Kinase Inhibitor for Overcoming Erlotinib Resistance in EGFR-Mutant Lung Cancer
Takayuki Nakagawa, Shinti Takeuchi, Tadaaki Yamada, Shigeki Nanjo, Daisuke Ishikawa, Takako Sanjo, Kenji Kita, Takahiro Nakamura, Kunio Matsumoto, Kenichi Suda, Tetsuya Mizudomi, Yoshitaka Sekido, Toshimitsu Uenaka, and Seiji Yano

#### 2158 Calcium Channel TRPV6 as a Potential Therapeutic Target in Estrogen Receptor-Negative Breast Cancer

#### 2169 A Cell-Penetrating Bispecific Antibody for Therapeutic Regulation of Intracellular Targets
Richard H. Weisbart, Joseph F. Gera, Grace Chan, James E. Hansen, Erica Li, Cheri Cloninger, Arnold J. Levine, and Robert N. Nishimura

#### 2174 PKCδ Regulates Death Receptor 5 Expression Induced by PS-341 through ATF4–ATF3/CHOP Axis in Human Lung Cancer Cells
Linyan Xu, Ling Su, and Xiangguo Liu

#### 2183 Active Efflux of Dasatinib from the Brain Limits Efficacy against Murine Glioblastoma: Broad Implications for the Clinical Use of Molecularly Targeted Agents
Sagar Agarwal, Rajendar K. Mittapalli, David M. Zellmer, Jose L. Gallardo, Randy Donelson, Charlie Seiler, Stacy A. Decker, Karen S. SantaCruz, Jenny L. Pokorny, Jann N. Sarkaria, William F. Elmquist, and John R. Ohlfest
Garcinol Regulates EMT and Wnt Signaling Pathways In Vitro and In Vivo, Leading to Anticancer Activity against Breast Cancer Cells
Aamir Ahmad, Sanila H. Sarkar, Bassam Bitar, Shadan Ali, Amro Aboukameel, Seema Sethi, Yiwei Li, Bin Bao, Dejuan Kong, Sanjeev Banerjee, Subhash B. Padhye, and Fazlul H. Sarkar

An Optical Probe for Noninvasive Molecular Imaging of Orthotopic Brain Tumors Overexpressing Epidermal Growth Factor Receptor
Richard S. Agnes, Ann-Marie Broome, Jing Wang, Anjali Verma, Kari Lavik, and James P. Basilion

Targeting the IKKβ/mTOR/VEGF Signaling Pathway as a Potential Therapeutic Strategy for Obesity-Related Breast Cancer
Chun-Te Chen, Yi Du, Hirohito Yamaguchi, Jung-Mao Hsu, Hsu-Ping Kuo, Gabriel N. Hortobagyi, and Mien-Chie Hung

FcRL5 as a Target of Antibody–Drug Conjugates for the Treatment of Multiple Myeloma

Antitumor Activity of Triolimus: A Novel Multidrug-Loaded Micelle Containing Paclitaxel, Rapamycin, and 17-AAG
Jason R. Hasenstein, Ho-Chul Shin, Kelsey Kasmerchak, Darya Buehler, Glen S. Kwon, and Kevin R. Kozak

Drug Resistance to Inhibitors of the Human Double Minute-2 E3 Ligase Is Mediated by Point Mutations of p53, but Can Be Overcome with the p53 Targeting Agent RITA
Richard J. Jones, Chad C. Bjorklund, Veerabhadran Baladandayuthapani, Deborah J. Kuhn, and Robert Z. Orlowski

Activation of IL-6R/JAK1/STAT3 Signaling Induces De Novo Resistance to Irreversible EGFR Inhibitors in Non–Small Cell Lung Cancer with T790M Resistance Mutation
Sun Mi Kim, Oh-Joon Kwon, Yun Kyoung Hong, Joo Hang Kim, Flavio Solca, Sang-Jun Ha, Ross A. Soo, James G. Christensen, Ji Hyun Lee, and Byoung Chul Cho

BAY 1000394, a Novel Cyclin-Dependent Kinase Inhibitor, with Potent Antitumor Activity in Mono- and in Combination Treatment upon Oral Application
Gerhard Siemeister, Ulrich Lücking, Antje M. Wengner, Philip Lienau, Wolfram Steinke, Christoph Schatz, Dominik Mumberg, and Karl Ziegelbauer

Epithelial Tissue Hyperplasia Induced by the RAF Inhibitor PF-04880594 Is Attenuated by a Clinically Well-Tolerated Dose of the MEK Inhibitor PD-0325901

Sorafenib-Induced Hepatocellular Carcinoma Cell Death Depends on Reactive Oxygen Species Production In Vitro and In Vivo
Romain Coriat, Carole Nicco, Christiane Chéraux, Olivier Mir, Jérôme Alexandre, Stanislas Ropert, Bernard Weill, Stanislas Chaussade, François Goldwasser, and Frédéric Batteux

Targeting the Glyoxalase Pathway Enhances TRAIL Efficacy in Cancer Cells by Downregulating the Expression of Antiapoptotic Molecules
Hiroya Taniguchi, Mano Horinaka, Tatsushi Yoshida, Kimihiro Yano, Ahmed E. Goda, Shusuke Yasuda, Miki Wakada, and Toshiyuki Sakai

Discordant Cellular Response to Presurgical Letrozole in Bilateral Synchronous ERþ Breast Cancers with a KRAS Mutation or FGFR1 Gene Amplification
Justin M. Balko, Ingrid A. Mayer, Melinda E. Sanders, Todd W. Miller, Maria G. Kuba, Ingrid M. Meszoely, Nikhil Wagle, Levi A. Garraway, and Carlos L. Arteaga
ABSTRACT

Cyclooxygenase-2 (COX-2) is upregulated in pancreatic ductal adenocarcinomas (PDAC). However, COX-2 inhibition has not shown significant improvements in the survival of patients with metastatic PDAC. The cell-intrinsic role of COX-2 in PDAC progression was tested using both loss-of-function and gain-of-function approaches. Cox-2 deletion significantly delays the development of PDAC in mice. However, all animals ultimately succumbed to PDACs, suggesting that tumors can compensate for COX-2 loss through other mechanisms. Using immunofluorescence, it was found that membrane-associated GRP78 expression was associated with poor prognosis in a number of human cancers and was recently identified as a critical factor in protecting cells from cell death, and also colocalized with P-AKT expression in tumors with COX-2 deletion. Together, these results suggest that, while anti-COX-2 therapy may delay the development and progression of PDAC, mechanisms known to increase chemoresistance through AKT activation must also be overcome. For details, see article by Hill and colleagues on page 2127.