## Highlights of This Issue 2075

### THERAPEUTIC DISCOVERY

#### 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

**Targeting TRAIL Death Receptor 4 with Trivalent DR4 Atrimer Complexes**

#### 2087

**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

**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. Menee, Han W. Tun, Gerardo Colon-Otero, Edith A. Perez, and John A. Copland

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

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

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

#### 2096

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

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

**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

**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

### PRECLINICAL DEVELOPMENT

#### 2105

**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. Mitapalli, 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

**Active Efflux of Dasatinib from the Brain Limits Efficacy against Murine Glioblastoma: Broad Implications for the Clinical Use of Molecularly Targeted Agents**
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Garcinol Regulates EMT and Wnt Signaling Pathways \textit{In Vitro} and \textit{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 \textit{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 100394, 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 \textit{In Vitro} and \textit{In Vivo}

Romain Coriat, Carole Nicco, Christiane Chérreau, 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 ER\textsuperscript{+} 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
ABOUT THE COVER

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 communofluorescence, 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 chemo resistance through AKT activation must also be overcome. For details, see article by Hill and colleagues on page 2127.
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11 (10)


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