Highlights of This Issue 1049

REVIEWS

1051 Attacking a Nexus of the Oncogenic Circuitry by Reversing Aberrant eIF4F-Mediated Translation
Peter B. Bitterman and Vitaly A. Polunovsky

1062 Immunotherapy of Cancer with 4-1BB
Dass S. Vinay and Byoung S. Kwon

THERAPEUTIC DISCOVERY

1071 Quantitative Proteomic Profiling Identifies Protein Correlates to EGFR Kinase Inhibition

1082 Hyperactivation of 4E-Binding Protein 1 as a Mediator of Biguanide-Induced Cytotoxicity during Glucose Deprivation
Junichi Matsuo, Yoshinori Tsukumo, Sakae Saito, Satomi Tsukahara, Junko Sakurai, Shigeo Sato, Hiromichi Kondo, Masaru Ushijima, Masaaki Matsuura, Toshiki Watanabe, and Akihiro Tomida

1092 Off-Target Function of the Sonic Hedgehog Inhibitor Cyclopamine in Mediating Apoptosis via Nitric Oxide-Dependent Neutral Sphingomyelinase 2/Ceramide Induction
Marisa Meyers-Needham, Jocelyn A. Lewis, Salih Gencer, R. David Sentelle, Sahar A. Saddoughi, Christopher J. Clarke, Yusuf A. Hannun, Haakan Norell, Telma Martins da Palma, Michael Nishimura, Jacqueline M. Kraveka, Zohreh Khavandgar, Monzur Murshed, M. Ozgur Cevik, and Besim Ogretmen

PRECLINICAL DEVELOPMENT

1103 Evading Pgp Activity in Drug-Resistant Cancer Cells: A Structural and Functional Study of Antitubulin Furan Metotica Compounds
Tam Luong Nguyen, Maria Rosaria Cera, Andrea Pinto, Leonardo Lo Presti, Ernest Hamel, Paola Conti, Rick Gussio, and Peter De Wulf

1112 JAK–STAT and JAK–PI3K–mTORC1 Pathways Regulate Telomerase Transcriptionally and Posttranslationally in ATL Cells
Osamu Yamada, Kohji Ozaki, Masaharu Akiyama, and Kiyotaka Kawauchi

1122 Obatoclax Interacts Synergistically with the Irreversible Proteasome Inhibitor Carfilzomib in GC- and ABC-DLBC Cells In Vitro and In Vivo
Girija Dasmahapatra, Dmitry Lembersky, Minkyeong P. Son, Hiral Patel, Derick Peterson, Elisa Attkisson, Richard I. Fisher, Jonathan W. Friedberg, Paul Dent, and Steven Grant

1133 The Effect of Different Linkers on Target Cell Catabolism and Pharmacokinetics/Pharmacodynamics of Trastuzumab Maytansinoid Conjugates
Hans K. Erickson, Gail D. Lewis Phillips, Douglas D. Leipold, Carmela A. Provenzano, Elaine Mai, Holly A. Johnson, Bert Gunter, Charlene A. Audette, Manish Gupta, Jan Pinkas, and Jay Tibbitts

1143 ERK Inhibition Overcomes Acquired Resistance to MEK Inhibitors
Georgia Hatzivassiliou, Bonnie Liu, Carol O’Brien, Jill M. Spoerke, Klaus P. Hoeflich, Peter M. Haverty, Robert Soriano, William F. Forrest, Sherry Heldens, Huiwen Chen, Karen Toy, Connie Ha, Wei Zhou, Kyung Song, Lori S. Friedman, Lukas C. Amler, Garret M. Hampton, John Moffat, Marcia Belvin, and Mark R. Lackner

1155 Triggering Fbw7-Mediated Proteasomal Degradation of c-Myc by Oridonin Induces Cell Growth Inhibition and Apoptosis
Hui-Lin Huang, Heng-You Weng, Lu-Qin Wang, Chun-Hong Yu, Qiao-Juan Huang, Pan-Pan Zhao, Jun-Zhi Wen, Hui Zhou, and Liang-Hu Qu
### miRNA-29b Suppresses Prostate Cancer Metastasis by Regulating Epithelial–Mesenchymal Transition Signaling

Peng Ru, Robert Steele, Philip Newhall, Nancy J. Phillips, Karoly Toth, and Ratna B. Ray

### Therapeutic Significance of Estrogen Receptor β Agonists in Gliomas

Gangadhara R. Sareddy, Binoj C. Nair, Vijay K. Gonugunta, Quan-guang Zhang, Andrew Brenner, Darrell W. Brann, Rajeshwar Rao Tekmal, and Ratna K. Vadlamudi

### Multiple Antigenic Peptides Based on H-2Kk-Restricted CTL Epitopes from Murine Heparanase Induce a Potent Antitumor Immune Response In Vivo

Xu-Dong Tang, Guo-Zhen Wang, Jun Guo, Mu-Han Li, Chuan Li, Ning Li, Ya-Ling Chao, Chang-Zhu Li, Yu-Yun Wu, Chang-Jiang Hu, Dian-Chun Fang, and Shi-Ming Yang

### Cotargeting MAPK and PI3K Signaling with Concurrent Radiotherapy as a Strategy for the Treatment of Pancreatic Cancer

Terence M. Williams, Athena R. Flecha, Paul Keller, Ashwin Ram, David Karnak, Stefanie Galbán, Craig J. Galbán, Brian D. Ross, Theodore S. Lawrence, Alnawaz Rehemtulla, and Judith Sebolt-Leopold

### About the Cover

Several allosteric MEK inhibitors are in clinical development and have been designed to treat patients with tumors harboring RAS/RAF pathway alterations. Acquired resistance to this class of inhibitors is a pressing clinical problem. To identify strategies to overcome this resistance, Hatzivassiliou and colleagues derived and characterized three independent MEK inhibitor-resistant cell lines. All of the resistant cell lines harbored mutations in the allosteric binding pocket of MEK that is targeted by arylamine MEK inhibitors. In all cases the MEK resistant cell lines retained their addiction to the MAPK pathway and remained sensitive to a selective inhibitor of the ERK1/2 kinases, suggesting a role for ERK inhibitors in combating or preventing MEK inhibitor resistance. For details, see article by Hatzivassiliou and colleagues on page 1143.