Highlights of This Issue 2283

SMALL MOLECULE THERAPEUTICS

Identification of Preferred Chemotherapeutics for Combining with a CHK1 Inhibitor
Yang Xiao, Judi Ramiscal, Kaska Kowanetz, Christopher Del Nagro, Shiva Malek, Marie Evangelista, Elizabeth Blackwood, Peter K. Jackson, and Thomas O’Brien

Gramicidin A Induces Metabolic Dysfunction and Energy Depletion Leading to Cell Death in Renal Cell Carcinoma Cells
Justin M. David, Tori A. Owens, Sonali P. Barwe, and Ayyappan K. Rajasekaran

Developing Lipid Nanoparticle-Based siRNA Therapeutics for Hepatocellular Carcinoma Using an Integrated Approach
Leiming Li, Rongqi Wang, Denise Wilcox, Aparna Sarthy, Xiaoyu Lin, Xiaoli Huang, Lu Tian, Prasad Dane, Robert D. Hubbard, Todd M. Hansen, Carol Wada, Xiaobin Zhao, William M. Kohlbrenner, Stephen W. Fesik, and Yu Shen

BAY 80-6946 Is a Highly Selective Intravenous PI3K Inhibitor with Potent p110α and p110δ Activities in Tumor Cell Lines and Xenograft Models
Ningshu Liu, Bruce R. Rowley, Cathy O. Bull, Claudia Schneider, Andrea Haegebarth, Christoph A. Schatz, Paul R. Fracasso, Dean P. Wilkie, Martin Hentemann, Scott M. Wilhelm, William J. Scott, Dominik Mumberg, and Karl Ziegelbauer

PRIMA-1met/APR-246 Displays High Antitumor Activity in Multiple Myeloma By Induction of p73 and Noxa
Manujendra N. Saha, Hua Jiang, Yijun Yang, Donna Reeco, and Hong Chang

Synergistic Targeting of PI3K/AKT Pathway and Androgen Receptor Axis Significantly Delays Castration-Resistant Prostate Cancer Progression In Vivo
Christine Thomas, Francois Lamoureux, Claire Crafter, Barry R. Davies, Eliana Beraldi, Ladan Fazli, Soojin Kim, Daksh Thaper, Martin E. Gleave, and Amina Zoubeidi

AMG 900, a Small-Molecule Inhibitor of Aurora Kinases, Potentiates the Activity of Microtubule-Targeting Agents in Human Metastatic Breast Cancer Models

UNC569, a Novel Small-Molecule Mer Inhibitor with Efficacy against Acute Lymphoblastic Leukemia In Vitro and In Vivo
Sandra Christoph, Deborah DeRyckere, Jennifer Schlegel, J. Kimble Frazer, Lance A. Batchelor, Alesia Y. Trakhimets, Susan Sather, Debra M. Hunter, Christopher T. Cummings, Jing Liu, Chao Yang, Dmitri Kireev, Catherine Simpson, Jacqueline Norris-Drouin, Emily A. Hull-Ryde, William P. Janzen, Gary L. Johnson, Xiaodong Wang, Stephen V. Frye, H. Shelton Earp III, and Douglas K. Graham

SK-216, an Inhibitor of Plasminogen Activator Inhibitor-1, Limits Tumor Progression and Angiogenesis
Takeshi Masuda, Noboru Hattori, Tadashi Senoo, Shin Akita, Nobuhisa Ishikawa, Kazunori Fujitaka, Yoshinori Haruta, Hiroshi Murai, and Nobuoki Kohno

Paclitaxel–Hyaluronic NanoConjugates Prolong Overall Survival in a Preclinical Brain Metastases of Breast Cancer Model
Rajendar K. Mittapalli, Xinli Liu, Chris E. Adkins, Mohamed I. Nounou, Kaci A. Bohn, Tori B. Terrell, Hussaini S. Qhattal, Werner J. Geldenhuys, Diane Palmieri, Patricia S. Steeg, Quentin R. Smith, and Paul R. Lockman

Isolation of a Novel Thioflavin S–Derived Compound That Inhibits BAG-1–Mediated Protein Interactions and Targets BRAF Inhibitor–Resistant Cell Lines
Marion Enthammer, Emmanouil S. Papadakis, Maria Salome Gachet, Martin Deutsch, Stefan Schweiger, Katarzyna Koziel, Muhammad Imitiaz Ashraf, Sana Khalid, Gerhard Wobler, Graham Packham, Ramsey I. Cutress, Hermann Stuppner, and Jakob Troppmair
The Novel ATP-Competitive Inhibitor of the MET Hepatocyte Growth Factor Receptor EMD1214063 Displays Inhibitory Activity against Selected MET-Mutated Variants

Michaela Medová, Benoît Pochon, Bruno Streit, Wiesława Blank-Liss, Paola Francica, Deborah Stroka, Adrian Keogh, Daniel M. Aebersold, Andrzej Blaukat, Friedhelm Bladt, and Yitzhak Zimmer

Characterization of a New Class of Androgen Receptor Antagonists with Potential Therapeutic Application in Advanced Prostate Cancer

Huiyang Li, Mohamed D.H. Hassona, Nathan A. Lack, Peter Axerio-Cilies, Eric Leblanc, Peyman Tavassoli, Natalia Kanaan, Kate Frewin, Kriti Singh, Hans Adomat, Konrad J. Böhm, Helge Prinz, Emma Tomlinson Guns, Paul S. Rennie, and Artem Cherkasov

177Lu-EC0800 Combined with the Antifolate Pemetrexed: Preclinical Pilot Study of Folate Receptor Targeted Radionuclide Tumor Therapy

Josefine Reber, Stephanie Haller, Christopher P. Leamon, and Cristina Muller

MTI-101 (Cyclized HYD1) Binds a CD44 Containing Complex and Induces Necrotic Cell Death in Multiple Myeloma

Anthony W. Gebhard, Priyesh Jain, Rajesh R. Nair, Michael F. Emmons, Raul F. Argilagos, John M. Koomen, Mark L. McLaughlin, and Lori A. Hazlehurst

A Highly Potent and Specific MET Therapeutic Protein Antagonist with Both Ligand-Dependent and Ligand-Independent Activity


Molecular Radiotherapy Using Cleavable Radioimmunoconjugates That Target EGFR and γH2AX

Bart Cornelissen, Andrew Waller, Sarah Able, and Katherine A. Vallis

A Highly Potent and Specific MET Therapeutic Protein Antagonist with Both Ligand-Dependent and Ligand-Independent Activity


Molecular Radiotherapy Using Cleavable Radioimmunoconjugates That Target EGFR and γH2AX

Bart Cornelissen, Andrew Waller, Sarah Able, and Katherine A. Vallis

PARP1 Is Overexpressed in Nasopharyngeal Carcinoma and Its Inhibition Enhances Radiotherapy

Jeremy P.H. Chow, Wing Yu Man, Mao Mao, Han Chen, Florence Cheung, John Nicholls, Sai Wah Tsao, Maria Li Lung, and Randy Y.C. Poon

CONCLUSION

PARP1 is overexpressed in nasopharyngeal carcinoma (NPC) and its inhibition enhances radiotherapy. PARP1 expression in NPC was significantly higher than in normal nasopharynx, and NPC cell lines expressing high levels of PARP1 were selected. PARP1 inhibition enhanced the radiosensitivity of NPC cell lines, but not of normal nasopharynx. PARP1 inhibition enhanced DNA double-strand breaks induction during radiotherapy, which was accompanied by the activation of p53 signaling, and this was associated with the enhancement of NPC cell killing. PARP1 inhibition also prevented the cell cycle check-point arrest at G2/M caused by radiation. The enhancement of radiosensitivity of NPC cells by PARP1 inhibition was associated with an increase in apoptosis, and this was linked to the activation of the intrinsic pathway of apoptosis. PARP1 inhibition also enhanced the expression of the radiosensitizer pimonidazole (Hb-P) and this was associated with an increase in hypoxia levels. In addition, PARP1 inhibition enhanced the expression of the radiosensitizer nitric oxide synthase (NOSIII) and this was associated with an increase in nitric oxide levels. In conclusion, PARP1 inhibition is a promising radiosensitizer for NPC and could be used in combination with radiotherapy.
miRNA-141, Downregulated in Pancreatic Cancer, Inhibits Cell Proliferation and Invasion by Directly Targeting MAP4K4
Gang Zhao, Bo Wang, Yang Liu, Jun-gang Zhang, Shi-chang Deng, Qi Qin, Kui Tian, Xiang Li, Shuai Zhu, Yi Niu, Qiong Gong, and Chun-you Wang

Arginine Deiminase Resistance in Melanoma Cells Is Associated with Metabolic Reprogramming, Glucose Dependence, and Glutamine Addiction
Yan Long, Wen-Bin Tsai, Medhi Wangpaichitr, Takashi Tsukamoto, Niramol Savaraj, Lynn G. Feun, and Macus Tien Kuo

Combining PARP-1 Inhibition and Radiation in Ewing Sarcoma Results in Lethal DNA Damage
Hae-June Lee, Changhwan Yoon, Benjamin Schmidt, Do Joong Park, Alexia Y. Zhang, Hayriye V. Erkizan, Jeffrey A. Toretsky, David G. Kirsch, and Sam S. Yoon

Capillary Isoelectric-Focusing Immunoassays to Study Dynamic Oncoprotein Phosphorylation and Drug Response to Targeted Therapies in Non-Small Cell Lung Cancer

EGFR Exon 20 Insertion A763-Y764insFQEA and Response to Erlotinib—Letter
Pei Jye Voon, Dana Wai Yi Tsui, Nitzan Rosenfeld, and Tan Min Chin

ABOUT THE COVER
Ribbon representation of a homology model of the c-Met specific Anticalin PRS-110. Anticals are engineered human lipocalins that represent a next generation class of drug molecules. The lipocalins have a structurally conserved β-barrel architecture that forms a cup-shaped ligand binding pocket that can accommodate small and large ligands. The β strands (blue) of the lipocalin form the base of the ligand-binding pocket and the entry of the pocket is comprised of four loops connecting the β strands. Novel, target-specific Anticals are generated by engineering mutations (pink regions, PRS-110 mutations) within these four loops and then selecting variants with the desired binding activity. For details, see article by Olwill and colleagues on page 2459.