Highlights of This Issue 339

CHEMICAL THERAPEUTICS

341 The HSP70 and Autophagy Inhibitor Pifithrin-μ Enhances the Antitumor Effects of TRAIL on Human Pancreatic Cancer
Hiroyuki Monma, Nanae Harashima, Touko Inao, Shinji Okano, Yoshitsugu Tajima, and Mamoru Harada

352 Tenovin-D3, a Novel Small-Molecule Inhibitor of Sirtuin SirT2, Increases p21 (CDKN1A) Expression in a p53-Independent Manner
Anna R. McCarthy, Marijke C.C. Sachweh, Maureen Higgins, Johanna Campbell, Catherine J. Drummond, Ingeborg M.M. van Leeuwen, Lisa Pirrie, Marcus J.G.W. Ladds, Nicholas J. Westwood, and Sonia Lain
See article, p. 471

361 Gossypin as a Novel Selective Dual Inhibitor of v-raf Murine Sarcoma Viral Oncogene Homolog B1 and Cyclin-Dependent Kinase 4 for Melanoma

373 Novel Inhibitors of Rad6 Ubiquitin Conjugating Enzyme: Design, Synthesis, Identification, and Functional Characterization
Matthew A. Sanders, Ghali Brahemi, Pratima Nangia-Makker, Vitaly Balan, Matteo Morelli, Hend Kothayer, Andrew D. Westwell, and Malathy P.V. Shekhar

SMALL MOLECULE THERAPEUTICS

384 HER2-Targeted Hybrid Peptide That Blocks HER2 Tyrosine Kinase Disintegrates Cancer Cell Membrane and Inhibits Tumor Growth In Vivo
Megumi Kawamoto, Tomohisa Horibe, Masayuki Kohno, and Koji Kawakami

LARGE MOLECULE THERAPEUTICS

394 Targeting IGF-IR with Ganitumab Inhibits Tumorigenesis and Increases Durability of Response to Androgen-Deprivation Therapy in VCaP Prostate Cancer Xenografts
Cale D. Fahrenholtz, Pedro J. Beltran, and Kerry L. Burnstein

405 Poly(β-amino ester) Nanoparticle Delivery of TP53 Has Activity against Small Cell Lung Cancer In Vitro and In Vivo
Chandrashekhar D. Kamat, Ron B. Shmueli, Nick Connis, Charles M. Rudin, Jordan J. Green, and Christine L. Hann

416 A Human Single-Domain Antibody Elicits Potent Antitumor Activity by Targeting an Epitope in Mesothelin Close to the Cancer Cell Surface
Zhewei Tang, Mingqian Feng, Wei Gao, Yen Phung, Weizao Chen, Amit Chaudhary, Brad St. Croix, Min Qian, Dimitar S. Dimitrov, and Mitchell Ho

427 Downregulation of HER3 by a Novel Antisense Oligonucleotide, EZN-3920, Improves the Antitumor Activity of EGFR and HER2 Tyrosine Kinase Inhibitors in Animal Models
Yaming Wu, Yixian Zhang, Maoliang Wang, Qi Li, Zhengxing Qu, Victoria Shi, Patricia Kraft, Steve Kim, Ying Gao, Jenny Pak, Stephen Youngster, Ivan D. Horak, and Lee M. Greenberger

CANCER THERAPEUTICS INSIGHTS

438 Transient Exposure to Quizartinib Mediates Sustained Inhibition of FLT3 Signaling while Specifically Inducing Apoptosis in FLT3-Activated Leukemia Cells
Ruwanthi N. Gunawardane, Ronald R. Nepomuceno, Allison M. Rooks, Jeremy P. Hunt, Jill M. Ricono, Barbara Belli, and Robert C. Armstrong
**GX15-070 (Obatoclax) Induces Apoptosis and Inhibits Cathepsin D- and L–Mediated Autophagosomal Lysis in Antiestrogen-Resistant Breast Cancer Cells**
Jessica L. Schwartz-Roberts, Ayesha N. Shajahan, Katherine L. Cook, Anni Warri, Mones Abu-Asab, and Robert Clarke

**Inhibition of HSP90 with AUY922 Induces Synergy in HER2-Amplified Trastuzumab–Resistant Breast and Gastric Cancer**

**Biological Characterization of TAK-901, an Investigational, Novel, Multitargeted Aurora B Kinase Inhibitor**
Pamela Farrell, Lihong Shi, Jennifer Matuszkiewicz, Deepika Balakrishna, Takashi Hoshino, Lilly Zhang, Sarah Elliott, Robyn Falbrey, Bumsup Lee, Petro Halkowycz, BiChing Sang, Seigo Ishino, Toshiyuki Nomura, Mika Teratani, Yoshikazu Ohta, Charles Grimshaw, Bheema Paraselli, Takashi Satou, and Ron de Jong

**Modulation of p53 C-Terminal Acetylation by mdm2, p14ARF, and Cytoplasmic SirT2**
Ingeborg M.M. van Leeuwen, Maureen Higgins, Johanna Campbell, Anna R. McCarthy, Marijke C.C. Sachweh, Ana Marin Navarro, and Sonia Lain
See article, p. 352

**Efficacy of Low-Dose Oral Metronomic Dosing of the Prodrug of Gemcitabine, LY2334737, in Human Tumor Xenografts**
Susan E. Pratt, Sara Durland-Busbice, Robert L. Shepard, Gregory P. Donoho, James J. Starling, Enaksha R. Wickremsinhe, Everett J. Perkins, and Anne H. Dantzig

**Tumor-Initiating Cells and FZD8 Play a Major Role in Drug Resistance in Triple-Negative Breast Cancer**

**Antitumor Effect of SIRT1 Inhibition in Human HCC Tumor Models In Vitro and In Vivo**
Simone Portmann, René Fahrner, Antje Lechleiter, Adrian Keogh, Sarah Overney, Alexander Laemmle, Kei Mikami, Matteo Montani, Mario P. Tschan, Daniel Candinas, and Deborah Stroka

**COMPANION DIAGNOSTICS & CANCER BIOMARKERS**

**Quantitative Chemical Proteomics Profiling Differentiates Erlotinib from Gefitinib in EGFR Wild-Type Non–Small Cell Lung Carcinoma Cell Lines**
Angélique Augustin, Jens Lamerz, Hélène Meistermann, Sabrina Golling, Stefan Scheiblich, Johannes C. Hermann, Guillaume Duchateau-Nguyen, Manuel Tzouros, David W. Avila, Hanno Langen, Laurent Essioux, and Barbara Klughammer

**Analysis of DNA Repair–Related Genes in Breast Cancer Reveals CUL4A Ubiquitin Ligase as a Novel Biomarker of Trabectedin Response**
María J. García, Laura Paula Saucedo-Cuevas, Iván Muñoz-Repeto, Victoria Fernández, María J. Robles, Samuel Domingo, José Palacios, Miguel Aracil, Antonio Nieto, Juan Carlos Tercero, and Javier Benítez

**Use of Molecular Biomarkers to Quantify the Spatial Distribution of Effects of Anticancer Drugs in Solid Tumors**
Jasdeep K. Saggar, Andrea S. Fung, Krupa J. Patel, and Ian F. Tannock
ABOUT THE COVER

The yeast Rad6 human homologues HHR6A and HHR6B (or Rad6A and Rad6B) encode ubiquitin-conjugating enzymes (or E2) that play a central role in substrate ubiquitination and E3 ligase selection. The ubiquitin-conjugating activity of Rad6 is essential for its function in postreplication DNA repair, damage-induced mutagenesis, and proteolysis. Using virtual screening of ZINC database against a pharmacophore model for consensus, E2-ubiquitin binding sites followed by biological evaluation of virtual hits, two small molecule compounds with a triazine core structure, and possessing Rad6 ubiquitin conjugation inhibitory activity were identified. These small molecules inhibit breast cancer cell proliferation, migration, and colony formation by blocking G2–M progression. For details, see article by Sanders and colleagues on page 373.