### Highlights of This Issue 515

#### REVIEWS

- **517** Mesothelin-Targeted Agents in Clinical Trials and in Preclinical Development  
  Ronan J. Kelly, Elad Sharon, Ira Pastan, and Raffit Hassan

- **526** Novel Therapies for Metastatic Renal Cell Carcinoma: Efforts to Expand beyond the VEGF/mTOR Signaling Paradigm  
  Sumanta Kumar Pal, Stephen Williams, David Y. Josephson, Courtney Carmichael, Nicholas J. Vogelzang, and David I. Quinn

- **538** The Ubiquitin-Proteasome System Meets Angiogenesis  
  Nader Rahimi

#### THERAPEUTIC DISCOVERY

- **549** The Antidiabetic Drug Metformin Inhibits Gastric Cancer Cell Proliferation *In Vitro and In Vivo*  
  Kiyohito Kato, Jian Gong, Hisakazu Iwama, Akira Kitakata, Joji Tani, Hisaaki Miyoshi, Kei Nomura, Shima Mimura, Mitsuyoshi Kobayashi, Yuichi Aritomo, Hideyuki Kobara, Hirohito Mori, Takashi Himoto, Keiichi Okano, Yasuyuki Suzuki, Koji Murao, and Tsutomu Masaki

- **561** Inhibition of p38 MAPK-Dependent Excision Repair Cross-Complementing 1 Expression Decreases the DNA Repair Capacity to Etoposide  
  Min-Shao Tsai, Shao-Hsing Weng, Huang-Jen Chen, Yu-Fan Chiu, Yu-Ching Huang, Sheng-Chieh Tseng, Ya-Hsun Kuo, and Yun-Wei Lin

- **572** Galiximab Signals B-NHL Cells and Inhibits the Activities of NF-κB–Induced YY1- and Snail-Resistant Factors: Mechanism of Sensitization to Apoptosis by Chemoinmunotherapeutic Drugs  
  Melisa A. Martinez-Paniagua, Mario I. Vega, Sara Huerta-Yepez, Stavroula Baritaki, Gabriel G. Vega, Kandasamy Hariharan, and Benjamin Bonavida

- **582** Antitumor Activity of a Novel Bispecific Antibody That Targets the ErbB2/ErbB3 Oncogenic Unit and Inhibits Heregulin-Induced Activation of ErbB3  
  Charlotte F. McDonagh, Alexandre Huhalov, Brian D. Harms, Sharlene Adams, Violette Paragas, Shinji Oyama, Bo Zhang, Lia Luus, Ryan Overland, Stephanie Nguyen, Jinning Gu, Neeraj Kohli, Matt Wallace, Michael J. Feldhaus, Arthur J. Kudla, Birgit Schoeberl, and Ulrik B. Nielsen

- **594** A Human Fab-Based Immunoconjugate Specific for the LMP1 Extracellular Domain Inhibits Nasopharyngeal Carcinoma Growth *In Vitro and In Vivo*  
  Renjie Chen, Dawei Zhang, Yuan Mao, Jin Zhu, Hao Ming, Juan Wen, Jun Ma, Qing Cao, Hong Lin, Qi Tang, Jie Liang, and Zhengqiu Feng

- **604** The Relationship of Thioredoxin-1 and Cisplatin Resistance: Its Impact on ROS and Oxidative Metabolism in Lung Cancer Cells  
  Medhi Wangpaichitr, Elizabeth J. Sullivan, George Theodoropoulos, Chunjing Wu, Min You, Lynn G. Feun, Theodore J. Lampidis, Macus T. Kuo, and Niramol Savaraj

- **629** Inhibition of dUTPase Induces Synthetic Lethality with Thymidylate Synthase–Targeted Therapies in Non–Small Cell Lung Cancer  
  Peter M. Wilson, Melissa J. Labonte, Heinz-Josef Lenz, Philip C. Mack, and Robert D. Ladner

- **639** DLK1 as a Potential Target against Cancer Stem/Progenitor Cells of Hepatocellular Carcinoma  
  Xiao Xu, Rui-Fang Liu, Xin Zhang, Li-Yu Huang, Fei Chen, Qian-Lan Fei, and Ze-Guang Han

- **639** 212 Pb-Radioimmunotherapy Induces G₀ Cell-Cycle Arrest and Delays DNA Damage Repair in Tumor Xenografts in a Model for Disseminated Intraperitoneal Disease  
  Kwon Joong Yong, Diane E. Milenic, Kwamena E. Baidoo, and Martin W. Brechbiel
PRECLINICAL DEVELOPMENT

649 | Potent Inhibition of Angiogenesis by the IGF-1 Receptor-Targeting Antibody SCH717454 Is Reversed by IGF-2
Hemant K. Bid, Jun Zhan, Doris A. Phelps, Raushan T. Kurmasheva, and Peter J. Houghton

660 | MET Activation Mediates Resistance to Lapatinib Inhibition of HER2-Amplified Gastric Cancer Cells
Chin-Tung Chen, Hyaehwan Kim, David Liska, Sizhi Gao, James G. Christensen, and Martin R. Weiser

670 | CEP-28122, a Highly Potent and Selective Orally Active Inhibitor of Anaplastic Lymphoma Kinase with Antitumor Activity in Experimental Models of Human Cancers
Mangeng Cheng, Matthew R. Quail, Diane E. Gingrich, Gregory R. Ott, Lihui Lu, Weihua Wan, Mark S. Albom, Thelma S. Angeles, Lisa D. Aimone, Flavio Cristofani, Rodolfo Machiorlatti, Cristina Abele, Mark A. Ator, Bruce D. Dorsey, Giorgio Inghirami, and Bruce A. Ruggeri

680 | Low-Dose Metronomic Oral Dosing of a Prodrug of Gemcitabine (LY2334737) Causes Antitumor Effects in the Absence of Inhibition of Systemic Vasculogenesis
Giulio Francia, Yuval Shaked, Kae Hashimoto, John Sun, Melissa Yin, Carolyn Costa, Ping Xu, Shan Man, Christina Hackl, Julie Stewart, Mark Uhlik, Anne H. Dantzig, F. Stuart Foster, and Robert S. Kerbel

690 | Ponatinib (AP24534), a Multitargeted Pan-FGFR Inhibitor with Activity in Multiple FGFR-Amplified or Mutated Cancer Models

700 | TAK-960, a Novel, Orally Available, Selective Inhibitor of Polo-Like Kinase 1, Shows Broad-spectrum Preclinical Antitumor Activity in Multiple Dosing Regimens
Yuichi Hikichi, Kohei Honda, Kouki Hikami, Hitoshi Miyashita, Isao Kaieda, Saomi Murai, Noriko Uchiyama, Maki Hasegawa, Tomohiro Kawamoto, Takashi Sato, Takashi Ichikawa, Sheldon Cao, Zhe Nie, Lilly Zhang, Johnny Yang, Keisuke Kuida, and Erik Kupperman

710 | An Integrated Genomic Approach to Identify Predictive Biomarkers of Response to the Aurora Kinase Inhibitor PF-03814735
Kenneth E. Hook, Scott J. Garza, Maruja E. Lira, Keith A. Ching, Nathan V. Lee, Joan Cao, Jing Yuan, Jingjing Ye, Mark Ozeck, Stephanie T. Shi, Xianxian Zheng, Paul A. Rejto, Julie L.C. Kan, James G. Christensen, and Adam Pavlicek

720 | Comprehensive Predictive Biomarker Analysis for MEK Inhibitor GSK1120212
Junping Jing, Joel Greshock, Joanna Dawn Holbrook, Aidan Gilmartin, Xiping Zhang, Elizabeth McNeil, Theresa Conway, Christopher Moy, Sylvie Laquerre, Kurt Bachman, Richard Wooster, and Yan Degenhardt

730 | The Novel Oral Hsp90 Inhibitor NVP-HSP9090 Exhibits Potent and Broad-spectrum Antitumor Activities In Vitro and In Vivo

740 | Molecular and Cellular Pharmacology of the Hypoxia-Activated Prodrug TH-302
Fanying Meng, James W. Evans, Deepthi Bhupathi, Monica Banica, Leslie Lan, Gustavo Lorente, Jian-Xin Duan, Xiaohong Cai, Alexandra M. Movday, Christopher P. Guise, Andrej Maroz, Robert F. Anderson, Adam V. Patterson, Gregory C. Stachelek, Peter M. Glazer, Mark D. Matteucci, and Charles P. Hart

750 | Effects of Anti-VEGF on Pharmacokinetics, Biodistribution, and Tumor Penetration of Trastuzumab in a Preclinical Breast Cancer Model
Cinthia V. Pastuskovas, Eduardo E. Mundo, Simon P. Williams, Tapan K. Nayak, Jason Ho, Sheila Ulufatu, Suzanna Clark, Sarajane Ross, Eric Cheng, Kathryn Parsons-Reponte, Gary Cain, Marjie Van Hoy, Nicholas Majidly, Sheila Bhedda, Josefa dela Cruz Chu, Katherine R. Kozak, Nicholas Lewin-Koh, Peter Nauka, Daniela Bumbaca, Mark Sliwkowski, Jay Tibbits, Frank-Peter Theil, Paul J. Fielder, Leslie A. Khawil, and C. Andrew Boswell
The Aurora Kinase A Inhibitor MLN8237 Enhances Cisplatin-Induced Cell Death in Esophageal Adenocarcinoma Cells
Vikas Sehdev, DunFa Peng, Mohammed Soutto, M. Kay Washington, Frank Revetta, Jeffrey Ecsedy, Alexander Zaika, Tilman T. Rau, Regine Schneider-Stock, Abbes Belkhiri, and Wael El-Rifai

MOLECULAR MEDICINE IN PRACTICE

Next Generation Sequencing of Prostate Cancer from a Patient Identifies a Deficiency of Methylthioadenosine Phosphorylase, an Exploitable Tumor Target

ABOUT THE COVER

The uracil-metabolizing enzyme dUTPase is a key component of de novo thymidine nucleotide biosynthesis and its expression is tightly regulated in replicating tissues such as the follicular germinal centers of human palatine tonsil (pictured). However, dUTPase is frequently overexpressed in human cancers and this has been firmly linked to drug resistance to chemotherapeutic agents that target thymidylate synthase (TS). Using immunohistochemistry and quantitative RT-PCR, evidence of dUTPase overexpression in a cohort of non-small cell lung cancers (NSCLC) was observed. Small interfering RNA-mediated gene silencing of dUTPase induced a strong synthetic lethal effect in NSCLC cell lines to two class-specific TS-targeted therapies including pemetrexed and fluorodeoxyuridine. Inhibition of dUTPase represents a promising, mechanism-based therapeutic approach to significantly enhance the efficacy of TS-targeted chemotherapeutic agents by overcoming a critical drug resistance pathway. For details, see article by Wilson and colleagues on page 616.