## Highlights of This Issue 515

### REVIEWS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>517</td>
<td>Mesothelin-Targeted Agents in Clinical Trials and in Preclinical Development</td>
<td>Ronan J. Kelly, Elad Sharon, Ira Pastan, and Raffit Hassan</td>
</tr>
<tr>
<td>526</td>
<td>Novel Therapies for Metastatic Renal Cell Carcinoma: Efforts to Expand beyond the VEGF/mTOR Signaling Paradigm</td>
<td>Sumanta Kumar Pal, Stephen Williams, David Y. Josephson, Courtney Carmichael, Nicholas J. Vogelzang, and David I. Quinn</td>
</tr>
<tr>
<td>538</td>
<td>The Ubiquitin-Proteasome System Meets Angiogenesis</td>
<td>Nader Rahimi</td>
</tr>
</tbody>
</table>

### THERAPEUTIC DISCOVERY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>549</td>
<td>The Antidiabetic Drug Metformin Inhibits Gastric Cancer Cell Proliferation In Vitro and In Vivo</td>
<td>Kiyohito Kato, Jian Gong, Hisakazu Iwama, Akira Kitana, Joji Tani, Hisaaki Miyoshi, Kei Nomura, Shima Mimura, Mitsuoshi Kobayashi, Yuiichi Aritomo, Hideyuki Kobara, Hirohito Mori, Takashi Himoto, Keichi Okano, Yasuyuki Suzuki, Koji Murao, and Tsutomu Masaki</td>
</tr>
<tr>
<td>561</td>
<td>Inhibition of p38 MAPK-Dependent Excision Repair Cross-Complementing 1 Expression Decreases the DNA Repair Capacity to Sensitize Lung Cancer Cells to Etoposide</td>
<td>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</td>
</tr>
<tr>
<td>572</td>
<td>Galiximab Signals B-NHL Cells and Inhibits the Activities of NF-κB-Induced YY1- and Snail-Resistant Factors: Mechanism of Sensitization to Apoptosis by Chemoimmunotherapeutic Drugs</td>
<td>Melisa A. Martinez-Paniagua, Mario I. Vega, Sara Huerta-Yepez, Stavroula Baritaki, Gabriol G. Vega, Kandasamy Haritharan, and Benjamin Bonavida</td>
</tr>
</tbody>
</table>

---

## Contents

The Cancer Drug Development Journal: From Concept to Clinic

March 2012 • Volume 11 • Number 3
PRECLINICAL DEVELOPMENT

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

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

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. Aitor, Bruce D. Dorsey, Giorgio Inghirami, and Bruce A. Ruggeri

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, Kei Hashimoto, John Sun, Melissa Yin, Carolyn Costa, Ping Xu, Shon Man, Christina Hackl, Julie Stewart, Mark Uhlik, Anne H. Dantzig, F. Stuart Foster, and Robert S. Kerbel

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

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

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, Jingjie Ye, Mark Ozeck, Stephanie T. Shi, Xianxian Zheng, Paul A. Rejto, Julie L.C. Kan, James G. Christensen, and Adam Pavlicek

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

The Novel Oral Hsp90 Inhibitor NVP-HSP990 Exhibits Potent and Broad-spectrum Antitumor Activities In Vitro and In Vivo

Molecular and Cellular Pharmacology of the Hypoxia-Activated Prodrug TH-302
Fanying Meng, James W. Evans, Deepthi Bhopathi, 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

Effects of Anti-VEGF on Pharmacokinetics, Biodistribution, and Tumor Penetration 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-Reponto, Gary Cain, Marije Van Hout, Nicholas Majidly, Sheila Bhedda,Josefa dela Cruz Chuh, Katherine R. Kozak, Nicholas Levent-Koh, Peter Nauka, Daniela Bumbaca, Mark Sliwkowski, Jay Tibbitts, 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

775 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.