

# DRUG METABOLISM AND DISPOSITION

A Publication of the American Society for Pharmacology and Experimental Therapeutics

September 2013

Vol. 41, No. 9

## CONTENTS

### PERSPECTIVE

- Critical Review of Preclinical Approaches to Investigate Cytochrome P450-Mediated Therapeutic Protein Drug-Drug Interactions and Recommendations for Best Practices: A White Paper. *Raymond Evers, Shannon Dallas, Leslie J. Dickmann, Odette A. Fahmi, Jane R. Kenny, Eugenia Kraynov, Theresa Nguyen, Aarti H. Patel, J. Greg Slatter, and Lei Zhang* . . . . . **1598**

### SHORT COMMUNICATIONS

- Atorvastatin Treatment Induces Uptake and Efflux Transporters in Human Liver. *Linda Björkhem-Bergman, Helena Bergström, Maria Johansson, Paolo Parini, Mats Eriksson, Anders Rane, and Lena Ekström* . . . . . **1610**

- The Human UDP-Glucuronosyltransferase UGT2A1 and UGT2A2 Enzymes Are Highly Active in Bile Acid Glucuronidation. *Martin Perreault, Louis Gauthier-Landry, Jocelyn Trottier, Mélanie Verreault, Patrick Caron, Moshe Finel, and Olivier Barbier* . . . . . **1616**

- Characterization of Microsomal Glutathione S-Transferases MGST1, MGST2, and MGST3 in Cynomolgus Macaque. *Yasuhiro Uno, Norie Murayama, Mutsuki Kunori, and Hiroshi Yamazaki* . . . . . **1621**

### ARTICLES

- Metabolism and Disposition of the Metabotropic Glutamate Receptor 5 Antagonist (mGluR5) Mavoglurant (AFQ056) in Healthy Subjects. *Markus Walles, Thierry Wolf, Yi Jin, Michael Ritzau, Luc Alexis Leuthold, Joel Krauser, Hans-Peter Gschwind, David Carcache, Matthias Kittelmann, Magdalena Ocwieja, Mike Ufer, Ralph Woessner, Abhijit Chakraborty, and Piet Swart* . . . **1626**

- Downregulation of Sulfotransferase Expression and Activity in Diseased Human Livers. *Emine B. Yalcin, Vijay More, Karissa L. Neira, Zhenqiang James Lu, Nathan J. Cherrington, Angela L. Slitt, and Roberta S. King* . . . . . **1642**

- The Relative Contributions of CYP3A4 and CYP3A5 to the Metabolism of Vinorelbine. *Ariel R. Topletz, Jennifer B. Dennison, Robert J. Barbuch, Chad E. Hadden, Stephen D. Hall, and Jamie L. Renbarger* . . . . . **1651**

- A Systematic Approach to Evaluate Herb-Drug Interaction Mechanisms: Investigation of Milk Thistle Extracts and Eight Isolated Constituents as CYP3A Inhibitors. *Scott J. Brantley, Tyler N. Graf, Nicholas H. Oberlies, and Mary F. Paine* . . . **1662**

- Formation of Threohydrobupropion from Bupropion Is Dependent on 11 $\beta$ -Hydroxysteroid Dehydrogenase 1. *Arne Meyer, Anna Vuorinen, Agnieszka E. Zielinska, Petra Strajhar, Gareth G. Lavery, Daniela Schuster, and Alex Odermatt* . . . . . **1671**

- An Assessment of Pharmacokinetics and Antioxidant Activity of Free Silymarin Flavonolignans in Healthy Volunteers: A Dose Escalation Study. *Hao-Jie Zhu, Bryan J. Brinda, Kenneth D. Chavin, Hilary J. Bernstein, Kennerly S. Patrick, and John S. Markowitz* . . . . . **1679**

- The Role of Human Cytochrome P450 Enzymes in the Formation of 2-Hydroxymetronidazole: CYP2A6 is the High Affinity (Low  $K_m$ ) Catalyst. *Robin E. Pearce, Michael Cohen-Wolkowicz, Mario R. Sampson, and Gregory L. Kearns* . . . . **1686**

- Intestinal First-Pass Metabolism by Cytochrome P450 and Not P-Glycoprotein Is the Major Barrier to Amprenavir Absorption. *Matthew B. Dufek, Arlene S. Bridges, and Dhiren R. Thakker* . . . . **1695**

Continued on next page

▣ Biotransformation of a Novel Positive Allosteric Modulator of Metabotropic Glutamate Receptor Subtype 5 Contributes to Seizure-Like Adverse Events in Rats Involving a Receptor Agonism-Dependent Mechanism. *Thomas M. Bridges, Jerri M. Rook, Meredith J. Noetzel, Ryan D. Morrison, Ya Zhou, Rocco D. Gogliotti, Paige N. Vinson, Zixiu Xiang, Carrie K. Jones, Colleen M. Niswender, Craig W. Lindsley, Shaun R. Stauffer, P. Jeffrey Conn, and J. Scott Daniels . . . . .* **1703**

Inhibition of Cytochrome P450 Enzymes by the *E*- and *Z*-Isomers of Norendoxifen. *Jinzhong Liu, Peter J. Flockhart, Deshun Lu, Wei Lv, Wenjie Jessie Lu, Xu Han, Mark Cushman, and David A. Flockhart. . . . .* **1715**

▣ Supplemental material is available online at <http://dmd.aspetjournals.org>.

*About the cover:* Proposed binding modes of R-bupropion and S-bupropion in the ligand-binding pocket of human 11b-HSD1. See article by Meyer et al. on page 1671 of this issue.