

# DRUG METABOLISM AND DISPOSITION

A Publication of the American Society for Pharmacology and Experimental Therapeutics

July 2010

Vol. 38, No. 7

## CONTENTS

### SHORT COMMUNICATIONS

Spironolactone and Canrenone Inhibit UGT2B7-Catalyzed Human Liver and Kidney Microsomal Aldosterone 18 $\beta$ -Glucuronidation: A Potential Drug Interaction. *Kathleen M. Knights, Kushari Bowalgha, and John O. Miners* . . . . . **1011**

Expression and Characterization of Dog Cytochrome P450 2A13 and 2A25 in Baculovirus-Infected Insect Cells. *Diansong Zhou, Alban J. Linnenbach, Ruifeng Liu, Rick A. Luzziotti, Jennifer J. Harris, Catherine L. Booth-Genthe, and Scott W. Grimm* . . . . . **1015**

Potential Application of d-Optimal Designs in the Efficient Investigation of Cytochrome P450 Inhibition Kinetic Models. *Kuresh A. Youdim, Anthony C. Atkinson, Maciej Patan, Barbara Bogacka, and Patrick J. Johnson* . . . . . **1019**

Hepatic Uptake of the Magnetic Resonance Imaging Contrast Agent Gd-EOB-DTPA: Role of Human Organic Anion Transporters. *Mirko Leonhardt, Markus Keiser, Stefan Oswald, Jens Kühn, Jia Jia, Markus Grube, Heyo K. Kroemer, Werner Siegmund, and Werner Weitschies* . . . . . **1024**

### ARTICLES

Interplay of Dissolution, Solubility, and Nonsink Permeation Determines the Oral Absorption of the Hedgehog Pathway Inhibitor GDC-0449 in Dogs: An Investigation Using Preclinical Studies and Physiologically Based Pharmacokinetic Modeling. *Harvey Wong, Frank-Peter Theil, Yong Cui, James C. Marsters, Jr., S. Cyrus Khojasteh, Laurent Vernillet, Hank La, Xiling Song, Hong Wang, Eric J. Morinello, Yuzhong Deng, and Cornelis E. C. A. Hop* . . . . . **1029**

Significant Increase in Phenacetin Oxidation on L382V Substitution in Human Cytochrome P450 1A2. *Qingbiao Huang and Grazyna D. Szklarz* . . . . . **1039**

In Vivo Responses of the Human and Murine Pregnane X Receptor to Dexamethasone in Mice. *Nico Scheer, Jillian Ross, Yury Kapelyukh, Anja Rode, and C. Roland Wolf* . . . . . **1046**

Vectorial Transport of Nucleoside Analogs from the Apical to the Basolateral Membrane in Double-Transfected Cells Expressing the Human Concentrative Nucleoside Transporter hCNT3 and the Export Pump ABCC4. *Maria Rius, Daniela Keller, Manuela Brom, Johanna Hummel-Eisenbeiss, Frank Lyko, and Dietrich Keppler* . . . . . **1054**

Transporter Studies with the 3-O-Sulfate Conjugate of 17 $\alpha$ -Ethinylestradiol: Assessment of Human Kidney Drug Transporters. *Yong-Hae Han, Dennis Busler, Yang Hong, Yuan Tian, Cliff Chen, and A. David Rodrigues* . . . . . **1064**

Transporter Studies with the 3-O-Sulfate Conjugate of 17 $\alpha$ -Ethinylestradiol: Assessment of Human Liver Drug Transporters. *Yong-Hae Han, Dennis Busler, Yang Hong, Yuan Tian, Cliff Chen, and A. David Rodrigues* . . . . . **1072**

Characterization of HKI-272 Covalent Binding to Human Serum Albumin. *Jianyao Wang, Xiao Xian Li-Chan, Jim Atherton, Lin Deng, Robert Espina, Linning Yu, Peter Horwatt, Steven Ross, Susan Lockhead, Syed Ahmad, Appavu Chandrasekaran, Aram Oganesian, JoAnn Scatina, Abdul Mutlib, and Rasmy Talaat* . . . . . **1083**

□ Confidence Assessment of the Simcyp Time-Based Approach and a Static Mathematical Model in Predict-

*Continued on next page*

ing Clinical Drug-Drug Interactions for Mechanism-Based CYP3A Inhibitors. <i>Ying-Hong Wang</i> . . . . .	<b>1094</b>	Contribution of Rat Pulmonary Metabolism to the Elimination of Lidocaine, Midazolam, and Nifedipine. <i>Makoto Aoki, Kazuho Okudaira, Makoto Haga, Ryuichiro Nishigaki, and Masahiro Hayashi</i> . . . . .	<b>1183</b>
Differential Roles of Phase I and Phase II Enzymes in 3,4-Methylenedioxymethamphetamine-Induced Cytotoxicity. <i>Irene Antolino-Lobo, Jan Meulenbelt, Sandra M. Nijmeijer, Peter Scherpenisse, Martin van den Berg, and Majorie B. M. van Duursen</i> . . . . .	<b>1105</b>	Metabolism and Disposition of [ <sup>14</sup> C]BMS-690514 after Oral Administration to Rats, Rabbits, and Dogs. <i>Haizheng Hong, Hong Su, Haojun Sun, Alban Allentoff, Ihoezo V. Ekhatu, Theodore Chando, Janet Caceres-Cortes, Vikram Roongta, Ramaswamy A. Iyer, W. Griffith Humphreys, and Lisa J. Christopher</i> . . . . .	<b>1189</b>
In Vitro-In Vivo Correlation and Translation to the Clinical Outcome for CJ-13,610, a Novel Inhibitor of 5-Lipoxygenase. <i>J. Matthew Hutzler, Collette D. Linder, Roger J. Melton, John Vincent, and J. Scott Daniels</i> . . . . .	<b>1113</b>	Identification of the Human Enzymes Responsible for the Enzymatic Hydrolysis of Acridinium Bromide. <i>Joan Albertí, Audrey Martinet, Sònia Sentellas, and Miquel Salvà</i> . . . . .	<b>1202</b>
Energy Restriction Does Not Compensate for the Reduced Expression of Hepatic Drug-Processing Genes in Mice with Aging. <i>Yu-Kun Jennifer Zhang, Kurt W. Saupe, and Curtis D. Klaassen</i> . . . . .	<b>1122</b>	Role of UDP-Glucuronosyltransferase Isoforms in 13- <i>cis</i> Retinoic Acid Metabolism in Humans. <i>Sophie E. Rowbotham, Nicola A. Illingworth, Ann K. Daly, Gareth J. Veal, and Alan V. Boddy</i> . . . . .	<b>1211</b>
Regioselective Glucuronidation of Tanshinone IIa after Quinone Reduction: Identification of Human UDP-Glucuronosyltransferases, Species Differences, and Interaction Potential. <i>Qiong Wang, Haiping Hao, Xuanxuan Zhu, Guo Yu, Li Lai, Yitong Liu, Yuxin Wang, Shan Jiang, and Guangji Wang</i> . . . . .	<b>1132</b>	▣ Efavirenz Primary and Secondary Metabolism In Vitro and In Vivo: Identification of Novel Metabolic Pathways and Cytochrome P450 2A6 as the Principal Catalyst of Efavirenz 7-Hydroxylation. <i>Evan T. Ogburn, David R. Jones, Andrea R. Masters, Cong Xu, Yingying Guo, and Zeruesenay Desta</i> . . . . .	<b>1218</b>
▣ Identification of the Human UDP-Glucuronosyltransferases Involved in the Glucuronidation of Combretastatin A-4. <i>Silvio Aprile, Erika Del Grosso, and Giorgio Grosa</i> . . . . .	<b>1141</b>	Quantitative Prediction of Intestinal Metabolism in Humans from a Simplified Intestinal Availability Model and Empirical Scaling Factor. <i>Keitaro Kadono, Takafumi Akabane, Kenji Tabata, Katsuhiko Gato, Shigeyuki Terashita, and Toshio Teramura</i> . . . . .	<b>1230</b>
Prediction of Human Intestinal First-Pass Metabolism of 25 CYP3A Substrates from In Vitro Clearance and Permeability Data. <i>Michael Gertz, Anthony Harrison, J. Brian Houston, and Aleksandra Galetin</i> . . . . .	<b>1147</b>	Cytochrome P450-Mediated Bioactivation of the Epidermal Growth Factor Receptor Inhibitor Erlotinib to a Reactive Electrophile. <i>Xiaohai Li, Theodore M. Kamenecka, and Michael D. Cameron</i> . . . . .	<b>1238</b>
Use of the Øie-Tozer Model in Understanding Mechanisms and Determinants of Drug Distribution. <i>Nigel J. Waters and Franco Lombardo</i> . . . . .	<b>1159</b>	Shared Regulation of <i>UGT1A7</i> by Hepatocyte Nuclear Factor (HNF) 1 $\alpha$ and HNF4 $\alpha$ . <i>Ursula Ehmer, Sandra Kalthoff, Tim O. Lankisch, Nicole Freiberg, Michael P. Manns, and Christian P. Strassburg</i> . . . . .	<b>1246</b>
Metabolism of Fostamatinib, the Oral Methylene Phosphate Prodrug of the Spleen Tyrosine Kinase Inhibitor R406 in Humans: Contribution of Hepatic and Gut Bacterial Processes to the Overall Biotransformation. <i>David J. Sweeny, Weiqun Li, Jeffrey Clough, Somasekhar Bhamidipati, Rajinder Singh, Gary Park, Muhammad Baluom, Elliott Grossbard, and David T.-W. Lau</i> . . . . .	<b>1166</b>	<b>ERRATA</b>	
The Nuclear Receptors Constitutive Active/Androstane Receptor and Pregnane X Receptor Activate the <i>Cyp2c55</i> Gene in Mouse Liver. <i>Yoshihiro Konno, Hiroki Kamino, Rick Moore, Fred Lih, Kenneth B. Tomer, Darryl C. Zeldin, Joyce A. Goldstein, and Masahiko Negishi</i> . . . . .	<b>1177</b>	Correction to “5'-Aminocarbonyl Phosphonates as New Zidovudine Depot Forms: Antiviral Properties, Intracellular Transformations, and Pharmacokinetic Parameters” . . . . .	<b>1258</b>
▣ Supplemental material is available online at <a href="http://dmd.aspetjournals.org">http://dmd.aspetjournals.org</a> .		Correction to “Quantifying the Metabolic Activation of Nevirapine in Patients by Integrated Applications of NMR and Mass Spectrometry” . . . . .	<b>1259</b>

About the cover: Simplified scheme describing EE2 disposition after oral administration with focus on transport of EE2-Sul. See the article by Han et al. on page 1064 of this issue.