

# DRUG METABOLISM AND DISPOSITION

A Publication of the American Society for Pharmacology and Experimental Therapeutics

November 2014

Vol. 42, No. 11

## CONTENTS

### SPECIAL SECTION ON DMPK OF THERAPEUTIC PROTEINS

Toward Sensitive and Accurate Analysis of Antibody Biotherapeutics by Liquid Chromatography Coupled with Mass Spectrometry. *Bo An, Ming Zhang, and Jun Qu* . . . . . **1858**

Application of FcRn Binding Assays to Guide mAb Development. *Amita Datta-Mannan and Victor J. Wroblewski* . . . . . **1867**

Biotransformation and In Vivo Stability of Protein Biotherapeutics: Impact on Candidate Selection and Pharmacokinetic Profiling. *Michael P. Hall* . . . . . **1873**

Subcutaneous Absorption of Biotherapeutics: Knowns and Unknowns. *Wolfgang F. Richter and Björn Jacobsen* . . . . . **1881**

Pharmacokinetic Modeling of the Subcutaneous Absorption of Therapeutic Proteins. *Leonid Kagan* . . . . . **1890**

□ Evaluation of Near Infrared Fluorescent Labeling of Monoclonal Antibodies as a Tool for Tissue Distribution. *Kip P. Conner, Brooke M. Rock, Gayle K. Kwon, Joseph P. Balthasar, Lubna Abuqayyas, Larry C. Wienkers, and Dan A. Rock* . . . . . **1906**

Absorption, Distribution, Metabolism, and Excretion Considerations for the Development of Antibody-Drug Conjugates. *Tae H. Han and Baiteng Zhao* . . . . . **1914**

### SHORT COMMUNICATIONS

□ Clinical CYP3A Inhibitor Alternatives to Ketocanazole, Clarithromycin and Itraconazole, Are Not Transported into the Liver by Hepatic Organic Anion Transporting Polypeptides and Organic Cation Transporter 1. *J. William Higgins, Alice B. Ke, and Maciej J. Zamek-Gliszczynski* . . . . . **1780**

□ Activity-Limiting Role of Molecular Size: Size-Dependency of Maximum Activity for P450

Inhibition as Revealed by qHTS Data. *Peter Buchwald* . . . . . **1785**

UDP-Glucuronosyltransferase 1a Enzymes Are Present and Active in the Mouse Blastocyst. *Abby C. Collier, Yasuhiro Yamauchi, Brittany L.M. Sato, Luc R.A. Rougée, and Monika A. Ward* . . . . **1921**

### ACCELERATED COMMUNICATION

Rapid Production of Novel Pre-MicroRNA Agent hsa-mir-27b in *Escherichia coli* Using Recombinant RNA Technology for Functional Studies in Mammalian Cells. *Mei-Mei Li, Wei-Peng Wang, Wen-Juan Wu, Min Huang, and Ai-Ming Yu* . . . . **1791**

### ARTICLES

□ CYP3A5 Genotype Impacts Maraviroc Concentrations in Healthy Volunteers. *Yanhui Lu, Edward J. Fuchs, Craig W. Hendrix, and Namandjé N. Bumpus* . . . . **1796**

□ In Vitro Assay of Six UDP-Glucuronosyltransferase Isoforms in Human Liver Microsomes, Using Cocktails of Probe Substrates and Liquid Chromatography–Tandem Mass Spectrometry. *Kyung-Ah Seo, Hyo-Ji Kim, Eun Sook Jeong, Nagi Abdalla, Chang-Soo Choi, Dong-Hyun Kim, and Jae-Gook Shin* . . . . . **1803**

In Silico Prediction of Major Drug Clearance Pathways by Support Vector Machines with Feature-Selected Descriptors. *Kouta Toshimoto, Naomi Wakayama, Makiko Kusama, Kazuya Maeda, Yuichi Sugiyama, and Yutaka Akiyama* . . . . . **1811**

Effects of Cytochrome P450 2C9 Polymorphism on Bosentan Metabolism. *Mengchun Chen, Youting Zhang, Peipei Pan, Li Wang, Yunyun Zhan, Hui Jin, Mengmin Xia, Xianqin Wang, Dapeng Dai, Jianping Cai, and Guoxin Hu* . . . . . **1820**

Adaptive Hepatic and Intestinal Alterations in Mice after Deletion of NADPH-Cytochrome P450 Oxidoreductase (Cpr) in Hepatocytes. *Xingguo Cheng, Jun Gu, and Curtis D. Klaassen* . . . . . **1826**

Continued on next page

- Evaluation of In Situ Generated Valproyl 1-*O*- $\beta$ -Acyl Glucuronide in Valproic Acid Toxicity in Sandwich-Cultured Rat Hepatocytes. *Jayakumar Surendraddoss, Thomas K. H. Chang, and Frank S. Abbott* . . . . . **1834**
- ☐ Endoxifen and Other Metabolites of Tamoxifen Inhibit Human Hydroxysteroid Sulfotransferase 2A1 (hSULT2A1). *Edwin J. Squirewell, Xiaoyan Qin, and Michael W. Duffel* . . . . . **1843**
- Selective Inhibition of Human Solute Carrier Transporters by Multikinase Inhibitors. *Rosie A. Johnston, Tristan Rawling, Ting Chan, Fanfan Zhou, and Michael Murray* . . . . . **1851**
- ☐ Metabolites in Safety Testing Assessment in Early Clinical Development: A Case Study with a Glucokinase Activator. *Raman Sharma, John Litchfield, Karen Atkinson, Heather Eng, Neeta B. Amin, William S. Denney, John C. Pettersen, Theunis C. Goosen, Li Di, Esther Lee, Jeffrey A. Pfefferkorn, Deepak K. Dalvie, and Amit S. Kalgutkar* . . . . . **1926**
- Altered CYP2C9 Activity Following Modulation of CYP3A4 Levels in Human Hepatocytes: an Example of Protein-Protein Interactions. *Diane Ramsden, Donald J. Tweedie, Tom S. Chan, and Timothy S. Tracy* . . . . . **1940**
- Human Small Intestinal Epithelial Cells Differentiated from Adult Intestinal Stem Cells as a Novel System for Predicting Oral Drug Absorption in Humans. *Toru Takenaka, Naomoto Harada, Jiro Kuze, Masato Chiba, Takahiro Iwao, and Tamihide Matsunaga* . . . . . **1947**
- Mechanistic Studies of the Cationic Binding Pocket of CYP2C9 In Vitro and In Silico: Metabolism of Nonionizable Analogs of Tienilic Acid. *Suzanne Tay, Hoa Le, Kevin A. Ford, Sid D. Nelson, S. Cyrus Khojasteh, and Peter M. Rademacher* . . . **1955**
- ☐ Novel Mechanism of Impaired Function of Organic Anion-Transporting Polypeptide 1B3 in Human Hepatocytes: Post-Translational Regulation of OATP1B3 by Protein Kinase C Activation. *John Powell, Taleah Farasyn, Kathleen Köck, Xiaojie Meng, Sonia Pahwa, Kim L. R. Brouwer, and Wei Yue* . . . . . **1964**
- ☐ Gene Variants in *CYP2C19* Are Associated with Altered In Vivo Bupropion Pharmacokinetics but Not Bupropion-Assisted Smoking Cessation Outcomes. *Andy Z. X. Zhu, Qian Zhou, Lisa Sanderson Cox, Jasjit S. Ahluwalia, Neal L. Benowitz, and Rachel F. Tyndale* . . . . . **1971**

**ERRATUM**

- Correction to “Drug-Induced Perturbations of the Bile Acid Pool, Cholestasis, and Hepatotoxicity: Mechanistic Considerations Beyond the Direct Inhibition of the Bile Salt Export Pump” . . . . . **1978**

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

*About the cover:* Time course of IR800-8C2 tissue exposures (2, 48 and 240 h) and vehicle control (C) measured by cross-sectional imaging in whole body slices. See the article by Conner et al., ([dx.doi.org/10.1124/dmd.114.060319](https://doi.org/10.1124/dmd.114.060319)).