

# DRUG METABOLISM AND DISPOSITION

A Publication of the American Society for Pharmacology and Experimental Therapeutics

August 2016

Vol. 44, No. 8

## CONTENTS

### SPECIAL SECTION ON EMERGING NOVEL ENZYME PATHWAYS IN DRUG METABOLISM

- Cytochrome P450 and Non-Cytochrome P450 Oxidative Metabolism: Contributions to the Pharmacokinetics, Safety, and Efficacy of Xenobiotics. *Robert S. Foti and Deepak K. Dalvie* . . . . . **1229**
- Prevalence of Non-Cytochrome P450-Mediated Metabolism in Food and Drug Administration-Approved Oral and Intravenous Drugs: 2006–2015. *Matthew A. Cerny* . . . . . **1246**
- Going Beyond Common Drug Metabolizing Enzymes: Case Studies of Biotransformation Involving Aldehyde Oxidase,  $\gamma$ -Glutamyl Transpeptidase, Cathepsin B, Flavin-Containing Monooxygenase, and ADP-Ribosyltransferase. *Peter W. Fan, Donglu Zhang, Jason S. Halladay, James P. Driscoll, and S. Cyrus Khojasteh* . . . . . **1253**
- Species Differences in the Oxidative Desulfurization of a Thiouracil-Based Irreversible Myeloperoxidase Inactivator by Flavin-Containing Monooxygenase Enzymes. *Heather Eng, Raman Sharma, Angela Wolford, Li Di, Roger B. Ruggeri, Leonard Buckbinder, Edward L. Conn, Deepak K. Dalvie, and Amit S. Kalgutkar* . . . . . **1262**
- Microbial Flavoprotein Monooxygenases as Mimics of Mammalian Flavin-Containing Monooxygenases for the Enantioselective Preparation of Drug Metabolites. *Turan Gul, Marzena Krzek, Hjalmar P. Permentier, Marco W. Fraaije, and Rainer Bischoff* . . . . . **1270**
- Optimization of the Expression of Human Aldehyde Oxidase for Investigations of Single-Nucleotide Polymorphisms. *Alessandro Foti, Tobias Hartmann, Catarina Coelho, Teresa Santos-Silva, Maria João Romão, and Silke Leimkühler* . . . . . **1277**
- VX-509 (Decemotinin)-Mediated CYP3A Time-Dependent Inhibition: An Aldehyde Oxidase Metabolite as a Perpetrator of Drug-Drug Interactions. *Craig Zetterberg, Francois Maltais, Leena Laitinen, Shengkai Liao, Hong Tsao, Ananthsrinivas Chakilam, and Niresh Hariparsad* . . . . . **1286**
- Evaluating the Disposition of a Mixed Aldehyde Oxidase/Cytochrome P450 Substrate in Rats with Attenuated P450 Activity. *Rachel D. Crouch, Ryan D. Morrison, Frank W. Byers, Craig W. Lindsley, Kyle A. Emmitte, and J. Scott Daniels* . . . . . **1296**
- Ocular Metabolism of Levobunolol: Historic and Emerging Metabolic Pathways. *Upendra A. Argikar, Jennifer L. Dumouchel, Christine E. Dunne, Chitra Saran, Amanda L. Cirello, and Mithat Gunduz* . . . . . **1304**
- Biotransformation Capacity of Carboxylesterase in Skin and Keratinocytes for the Penta-Ethyl Ester Prodrug of DTPA. *Jing Fu, Matthew Sadgrove, Lesley Marson, and Michael Jay* . . . . . **1313**
- Nonclinical Pharmacokinetics, Disposition, and Drug-Drug Interaction Potential of a Novel D-Amino Acid Peptide Agonist of the Calcium-Sensing Receptor AMG 416 (Etelcalcetide). *Raju Subramanian, Xiaochun Zhu, Savannah J. Kerr, Joel D. Esmay, Steven W. Louie, Katheryne Z. Edson, Sarah Walter, Michael Fitzsimmons, Mylo Wagner, Marcus Soto, Roger Pham, Sarah F. Wilson, and Gary L. Skiles* . . . . . **1319**
- Phosphocholine Conjugation: An Unexpected In Vivo Conjugation Pathway Associated with Hepatitis C NS5B Inhibitors Featuring A Bicyclo[1.1.1]-Pentane. *Xiaoliang Zhuo, Joseph L. Cantone, Yingzi Wang, John E. Leet, Dieter M. Drexler, Kap-Sun Yeung, Xiaohua Stella Huang, Kyle J. Eastman, Kyle E. Parcella, Kathleen W. Mosure, Matthew G. Soars, John F. Kadow, and Benjamin M. Johnson* . . . . . **1332**
- Discovery of a Novel Microsomal Epoxide Hydrolase-Catalyzed Hydration of a Spiro Oxetane. *Xue-Qing Li, Martin A. Hayes, Gunnar Grönberg, Kristina Berggren, Neal Castagnoli, Jr., and Lars Weidolf* . . . . . **1341**
- Biotransformation and Rearrangement of Laromustine. *Alaa-Eldin F. Nassar, Adam V. Wisnewski, and Ivan King* . . . . . **1349**

Continued on next page

**PERSPECTIVE**

- S Evaluation of a New Molecular Entity as a Victim of Metabolic Drug-Drug Interactions—an Industry Perspective. *Tonika Bohnert, Aarti Patel, Ian Templeton, Yuan Chen, Chuang Lu, George Lai, Louis Leung, Susanna Tse, Heidi J Einolf, Ying-Hong Wang, Michael Sinz, Ralph Stearns, Robert Walsky, Wanping Geng, Sirimas Sudsakorn, David Moore, Ling He, Jan Wahlstrom, Jim Keirns, Rangaraj Narayanan, Dieter Lang, and Xiaoqing Yang; International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Victim Drug-Drug Interactions Working Group* . . . . . **1399**

**ARTICLES**

- S Metabolism and Disposition of Hepatitis C Polymerase Inhibitor Dasabuvir in Humans. *Jianwei Shen, Michael Serby, Aimee Reed, Anthony J. Lee, Rajeev Menon, Xiaomei Zhang, Kennan Marsh, Xia Wan, Olga Kavetskaia, and Volker Fischer* . . . . . **1139**
- S Metabolism and Disposition of Pan-Genotypic Inhibitor of Hepatitis C Virus NS5A Ombitasvir in Humans. *Jianwei Shen, Michael Serby, Bruce Surber, Anthony J. Lee, Junli Ma, Prajakta Badri, Rajeev Menon, Olga Kavetskaia, Sonia M. de Morais, Jens Sydor, and Volker Fischer* . . . . . **1148**
- Differences in Gene Regulation by Dual Ligands of Nuclear Receptors Constitutive Androstane Receptor (CAR) and Pregnane X Receptor (PXR) in HepG2 Cells Stably Expressing CAR/PXR. *Yuichiro Kanno, Nobuaki Tanuma, Saki Yazawa, Shuai Zhao, Miki Inaba, Satoshi Nakamura, Kiyomitsu Nemoto, and Yoshio Inouye* . . . . . **1158**
- S Metabolism and Disposition of the Hepatitis C Protease Inhibitor Paritaprevir in Humans. *Jianwei Shen, Michael Serby, Aimee Reed, Anthony J. Lee, Xiaomei Zhang, Kennan Marsh, Amit Khatri, Rajeev Menon, Olga Kavetskaia, and Volker Fischer* . . . . . **1164**
- S Effects of Chronic Renal Failure on Brain Cytochrome P450 in Rats. *Judith Naud, Jessica Harding, Caroline Lamarche, Stephanie Beauchemin, Francois A. Leblond, and Vincent Pichette* . . . . . **1174**
- S Difference in the Pharmacokinetics and Hepatic Metabolism of Antidiabetic Drugs in Zucker Diabetic Fatty and Sprague-Dawley Rats. *Xin Zhou, Luc R. A. Rougée, David W. Bedwell, Jeff W. Cramer, Michael A. Mohutsky, Nathan A. Calvert, Richard D. Moulton, Kenneth C. Cassidy, Nathan P. Yumibe, Lisa A. Adams, and Kenneth J. Ruterbories* . . . . . **1184**

- S Correlation of Cytochrome P450 Oxidoreductase Expression with the Expression of 10 Isoforms of Cytochrome P450 in Human Liver. *Hai-Feng Zhang, Zhi-Hui Li, Jia-Yu Liu, Ting-Ting Liu, Ping Wang, Yan Fang, Jun Zhou, Ming-Zhu Cui, Na Gao, Xin Tian, Jie Gao, Qiang Wen, Lin-Jing Jia, and Hai-Ling Qiao* . . . . . **1193**
- S Metabolic Disposition of Osimertinib in Rats, Dogs, and Humans: Insights into a Drug Designed to Bind Covalently to a Cysteine Residue of Epidermal Growth Factor Receptor. *Paul A. Dickinson, Mireille V. Cantarini, Jo Collier, Paul Frewer, Scott Martin, Kathryn Pickup, and Peter Ballard* . . . . . **1201**
- Use of Human Plasma Samples to Identify Circulating Drug Metabolites that Inhibit Cytochrome P450 Enzymes. *Heather Eng and R. Scott Obach* . . . . . **1217**
- Clopidogrel Markedly Increases Plasma Concentrations of CYP2C8 Substrate Pioglitazone. *Matti K. Ikonen, Alekski Tornio, Mikko Neuvonen, Pertti J. Neuvonen, Mikko Niemi, and Janne T. Backman* . . . . . **1364**
- S Application of Static Models to Predict Midazolam Clinical Interactions in the Presence of Single or Multiple Hepatitis C Virus Drugs. *Yaofeng Cheng, Li Ma, Shu-Ying Chang, W. Griffith Humphreys, and Wenyong Li* . . . . . **1372**
- S Impact of Experimental Conditions on the Evaluation of Interactions between Multidrug and Toxin Extrusion Proteins and Candidate Drugs. *Christian Lechner, Naoki Ishiguro, Ayano Fukuhara, Hidetada Shimizu, Naoko Ohtsu, Masahito Takatani, Kotaro Nishiyama, Ikumi Washio, Norio Yamamura, and Hiroyuki Kusuvara* . . . . . **1381**
- S Establishment of In Silico Prediction Models for CYP3A4 and CYP2B6 Induction in Human Hepatocytes by Multiple Regression Analysis Using Azole Compounds. *Mika Nagai, Yoshihiro Konno, Masahiro Satsukawa, Shinji Yamashita, and Kouichi Yoshinari* . . . . . **1390**
- S Selective Time- and NADPH-Dependent Inhibition of Human CYP2E1 by Clomethiazole. *David M. Stresser, Elke S. Perloff, Andrew K. Mason, Andrew P. Blanchard, Shangara S. Dehal, Timothy P. Creegan, Ritu Singh, and Eric T. Gangl* . . . . . **1424**

- ☐ A Pharmacokinetic Modeling Approach to Predict the Contribution of Active Metabolites to Human Efficacious Dose. *Iain J. Martin, Susan E. Hill, James A. Baker, Sujal V. Deshmukh, and Erin F. Mulrooney* . . . . . **1435**

**SHORT COMMUNICATIONS**

- ☐ Recommendation to Exclude Bile-Duct-Cannulated Rats with Hyperbilirubinemia for Proper Conduct of Biliary Drug Excretion Studies. *Koji Kato, Yoshitaka Hasegawa, Katsuya Iwata, Takuya Ichikawa, Tohru Yahara, Satoshi Tsuji, Masayuki Sugiura, and Jun-ichi Yamaguchi* . . . . . **1180**

- ☐ Application of Osmotic Pumps for Sustained Release of 1-Aminobenzotriazole and Inhibition of Cytochrome P450 Enzymes in Mice: Model Comparison with the Hepatic P450 Reductase Null Mouse. *Rowan A. Stringer, Suzie Ferreira, Jonathan Rose, and Sebastien Ronseaux* . . . . . **1213**

- ☐ Transcriptional Regulation of Cytosolic Sulfotransferase 1C2 by Vitamin D Receptor in LS180 Human Colorectal Adenocarcinoma Cells. *Kathleen G. Barrett, Hailin Fang, Thomas A. Kocarek, and Melissa Runge-Morris* . . . . . **1431**

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

*About the cover:* Fractional assignment of FDA-approved intravenous and orally administered small-molecule drugs meeting acceptance criteria for 2006–2015 which have no major metabolites or whose metabolites are formed by P450 by specific non-P450 enzymes. See the article by Cerny ([dx.doi.org/10.1124/dmd.116.070763](http://dx.doi.org/10.1124/dmd.116.070763)).