

DRUG METABOLISM AND DISPOSITION

A Publication of the American Society for Pharmacology and Experimental Therapeutics

April 2018

Vol. 46, No. 4

CONTENTS

EDITORIAL

Publishing in an ASPET Journal – What’s in It for You?. *Mary Vore* 440

ARTICLES

Regulation of Drug Metabolism by the Interplay of Inflammatory Signaling, Steatosis, and Xeno-Sensing Receptors in HepaRG Cells. *Norman Tanner, Lisa Kubik, Claudia Luckert, Maria Thomas, Ute Hofmann, Ulrich M. Zanger, Linda Böhmert, Alfonso Lampen, and Albert Braeuning* 326

Metabolic Profiling of the Novel Hypoxia-Inducible Factor 2 α Inhibitor PT2385 In Vivo and In Vitro. *Cen Xie, Xiaoxia Gao, Dongxue Sun, Youbo Zhang, Kristopher W. Krausz, Xuemei Qin, and Frank J. Gonzalez* 336

A Study on Pharmacokinetics of Bosentan with Systems Modeling, Part 1: Translating Systemic Plasma Concentration to Liver Exposure in Healthy Subjects. *Rui Li, Mark Niosi, Nathaniel Johnson, David A. Tess, Emi Kimoto, Jian Lin, Xin Yang, Keith A. Riccardi, Sangwoo Ryu, Ayman F. El-Kattan, Tristan S. Maurer, Larry M. Tremaine, and Li Di* 346

A Study on Pharmacokinetics of Bosentan with Systems Modeling, Part 2: Prospectively Predicting Systemic and Liver Exposure in Healthy Subjects. *Rui Li, Emi Kimoto, Mark Niosi, David A. Tess, Jian Lin, Larry M. Tremaine, and Li Di* 357

Polymorphic Human Sulfotransferase 2A1 Mediates the Formation of 25-Hydroxyvitamin D₃-3-O-Sulfate, a Major Circulating Vitamin D Metabolite in Humans. *Timothy Wong, Zhican Wang, Brian D. Chapron, Mizuki Suzuki, Katrina G. Claw, Chunying Gao, Robert S. Foti, Bhagwat Prasad, Alenka Chapron, Justina Calamia, Amarjit Chaudhry, Erin G. Schuetz, Ronald L. Horst, Qingcheng Mao, Ian H. de Boer, Timothy A. Thornton, and Kenneth E. Thummel* 367

CYP2J2 Expression in Adult Ventricular Myocytes Protects Against Reactive Oxygen Species Toxicity. *Eric A. Evangelista, Rozenn N. Lemaitre, Nona Sotoodehnia, Sina A. Gharib, and Rheem A. Totah* 380

Direct Quantification of Cytochromes P450 and Drug Transporters—A Rapid, Targeted Mass Spectrometry-Based Immunoassay Panel for Tissues and Cell Culture Lysates. *Frederik Weiß, Helen S. Hammer, Kathrin Klein, Hannes Planatscher, Ulrich M. Zanger, Agneta Norén, Christine Wegler, Per Artursson, Thomas O. Joos, and Oliver Poetz* 387

Role of c-Jun-N-Terminal Kinase in Pregnane X Receptor-Mediated Induction of Human Cytochrome P4503A4 In Vitro. *Guncha Taneja, Chun Chu, Paramahansa Maturu, Bhagavatula Moorthy, and Romi Ghose* 397

Simultaneous Assessment In Vitro of Transporter and Metabolic Processes in Hepatic Drug Clearance: Use of a Media Loss Approach. *James Harrison, Tom De Bruyn, Adam S. Darwich, and J. Brian Houston* 405

Comparison of Species and Cell-Type Differences in Fraction Unbound of Liver Tissues, Hepatocytes, and Cell Lines. *Keith Riccardi, Sangwoo Ryu, Jian Lin, Phillip Yates, David Tess, Rui Li, Dhirender Singh, Brian R. Holder, Brendon Kapinos, George Chang, and Li Di* 415

Maternal-Fetal Disposition and Metabolism of Retrosine in Pregnant Rats. *Xia Li, Xiaojing Yang, E Xiang, Jinyuan Luo, Shuaikai Qiu, Yan Fang, Li Zhang, Yu Guo, Jiang Zheng, and Hui Wang* 422

Metabolism and Disposition of a Novel Selective α 7 Neuronal Acetylcholine Receptor Agonist ABT-126 in Humans: Characterization of the Major Roles for Flavin-Containing Monooxygenases and UDP-Glucuronosyl Transferase 1A4 and 2B10 in Catalysis. *Hong Liu, David M. Stresser, Melissa J. Michmerhuizen, Xiaofeng Li, Ahmed A. Othman, Aimee D. Reed, Michael R. Schrimpf, Jens Sydor, and Anthony J. Lee* 429

Continued on next page

☐ Identification of Ketene-Reactive Intermediate of Erlotinib Possibly Responsible for Inactivation of P450 Enzymes. <i>Huimin Zhao, Siyuan Li, Zixin Yang, Ying Peng, Xiaohui Chen, and Jiang Zheng</i>	442
☐ LC-MS Differential Analysis for Fast and Sensitive Determination of Biotransformation of Therapeutic Proteins. <i>Ming Yao, Bingming Chen, Weiping Zhao, John T. Mehl, Lingjun Li, and Mingshe Zhu</i>	451
Mathematical and Experimental Validation of Flux Dialysis Method: An Improved Approach to Measure Unbound Fraction for Compounds with High Protein Binding and Other Challenging Properties. <i>J. Cory Kalvass, Colin Phipps, Gary J. Jenkins, Patricia Stuart, Xiaomei Zhang, Lance Heinle, Marjoleen J. M. A. Nijsen, and Volker Fischer</i>	458
☐ Identification of Galeterone and Abiraterone as Inhibitors of Dehydroepiandrosterone Sulfonation Catalyzed by Human Hepatic Cytosol, SULT2A1, SULT2B1b, and SULT1E1. <i>Caleb Keng Yan Yip, Sumit Bansal, Siew Ying Wong, and Aik Jiang Lau</i>	470

ERRATA

Correction to “A Study on Pharmacokinetics of Bosentan with Systems Modeling, Part 1: Translating Systemic Plasma Concentration to Liver Exposure in Healthy Subjects”	483
Correction to “A Study on Pharmacokinetics of Bosentan with Systems Modeling, Part 2: Prospectively Predicting Systemic and Liver Exposure in Healthy Subjects”	484

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

About the cover: Heat-map visualization of the expression of cytochrome P450 (CYP) genes in HepaRG cells and their regulation by nuclear receptor agonists (5 μ M 3MC, 5 μ M CITCO, 10 μ M Rif, 30 μ M tBHQ, 50 μ M Wy), O/P (125 μ M each), and IL-6 (10 ng/mL). See the article by Braeuning et al. ([dx.doi.org/10.1124/dmd.117.078675](https://doi.org/10.1124/dmd.117.078675).)