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Special Section on Bile Acids, Drug Metabolism, and Toxicity—Editorial

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This issue of Drug Metabolism and Disposition presents a special section on "Bile Acids, Drug Metabolism, and Toxicity," contributed by Dr. Curtis D. Klaassen and some of his former trainees. Dr. Klaassen spent 45 years at the University of Kansas School of Medicine, teaching pharmacology and toxicology to medical, nursing, and graduate students, as well as serving as a university-distinguished professor and chair of the Department of Pharmacology, Toxicology, and Therapeutics. His scholarly and educational accomplishments left a broad impact on the advancement of pharmacology and toxicology. In his career, he has published more than 600 manuscripts. He ranks as one of the most cited researchers in the field of pharmacology and toxicology, with more than 96,000 citations and an *h*-index of 129. He has made significant contributions in several areas, including the hepatic uptake and biliary excretion of drugs and other xenobiotics (Klaassen and Aleksunes, 2010; Cui et al., 2012); the roles of metallothionein in the hepatotoxicity and nephrotoxicity of cadmium (Klaassen et al., 1999; Habeebu et al., 2000; Park et al., 2002); the effects of endocrine disrupters on the disposition of thyroid hormones (Martin and Klaassen, 2010; Richardson and Klaassen, 2010); the mechanisms of nuclear receptors, especially pregnane X receptor (PXR), in the regulation of xenobiotic transporters in liver and kidney (Maher et al., 2005; Cui et al., 2010; Cui and Klaassen, 2016); the importance of nuclear factor erythroid 2-related factor 2 (NRF2) in adaptation to chemical and oxidative stress (Wu et al., 2012; Zhang et al., 2013); and the roles of bile acids in drug metabolism and toxicity (Iga and Klaassen, 1982; Csanaky et al., 2011; Selwyn et al., 2015).

Dr. Klaassen has received over forty national or international awards for his scholarly accomplishments. These included the Distinguished Professor Award from the University of Kansas, the Merit Award from the Society of Toxicology, the Merit Award from the International Union of Toxicology, and the Bernard B. Brodie Award from the Division for Drug Metabolism and Disposition of the American Society of Pharmacology and Experimental Therapeutics (ASPET) (Fig. 1). The Society of Toxicology also bestowed on him the Achievement Award (1976) and the Education Award (1993). In 2018, he was elected as a Fellow of the American Association for the Study of Liver Diseases (AASLD) and in 2020 was honored as a Fellow of ASPET.

In this special section, Dr. Klaassen, together with Dr. Supratim Choudhuri, contributes a comprehensive review article on the molecular regulation of bile acid homeostasis (Choudhuri and Klaassen, 2022), covering bile acid synthesis, the role of bile acid transporters in the enterohepatic circulation of bile acids, the role of a nuclear receptor farnesoid X receptor (FXR) on the regulation of bile acid synthesis and transporters, and the importance of bile acids in activating G-protein–coupled receptor signaling to modify intermediary metabolism. Dr. Choudhuri was a postdoctoral fellow with Dr. Klaassen, later becoming a Research Assistant Professor, at the University of Kansas. Currently, Dr. Choudhuri is a lead toxicologist and team leader in the Office of Food Additive Safety at the Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration.

Dr. Klaassen trained 120 Ph.D. students or postdoctoral fellows during his academic career. Many of his students have become national and international leaders in the field. Five of his students contributed one or two articles to this special section.

Dr. Grace L. Guo obtained her Ph.D. degree with Dr. Klaassen and did postdoctoral training with Dr. Frank Gonzales at the National Cancer Institute. Her faculty career began at the University of Kansas School of Medicine. Currently, she is a professor of pharmacology and toxicology at the Earnest Mario School of Pharmacy of Rutgers University. Since 2004, the Guo laboratory has contributed significantly in two areas: tissue specific functions of FXR (Thomas et al., 2010; Kong et al., 2012; Stofan and Guo, 2020) and gut-liver crosstalk by the bile acids-FXR-fibroblast growth factor 15/19 pathway in the regulation of bile acid synthesis and liver regeneration (Schumacher and Guo, 2019; Schumacher et al., 2020). In this special section, Dr. Guo's group provides a review article on environmental chemical contribution to the modulation of bile acid homeostasis via the FXR signaling pathway (Taylor et al., 2022). The article discusses how environmental chemicals contribute to the dysregulation of bile acid homeostasis and promote the development of liver diseases. Additionally, her group contributes a research article to depict the effect on hepatic drug metabolism by overexpression of fibroblast growth factor 15/19, which is associated with lowered growth hormone signaling (Rizzolo et al., 2022).

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ABBREVIATIONS: ASPET, American Society of Pharmacology and Experimental Therapeutics; FXR, farnesoid X receptor; NRF2, nuclear factor erythroid 2-related factor 2; PXR, pregnane X receptor.

Fig. 1. Dr. Curtis D. Klaassen was the recipient of the Bernard B. Brodie Award in Drug Metabolism and Disposition, awarded by the Division for Drug Metabolism and Disposition (DMDD) of the American Society for Pharmacology and Experimental Therapeutics (ASPET), in 2008. Photos are reproduced with permission from Dr. Curtis Klaassen.

Dr. Julia Y. Cui received her Ph.D. degree and did postdoctoral training with Dr. Klaassen. She started her independent academic career at the University of Washington in Seattle and is currently an Associate Professor of toxicology with a research focus on nuclear receptors and xenobiotic metabolism. In this special section, Dr. Cui's group provides a review on PXR and the gut-liver axis (Dutta et al., 2022). With advancement of genome-wide approaches, the article provides novel view on PXR-DNA interaction patterns for host genes and intestinal bacteria, as well as key PXR modulators in control of microbial metabolites under various physiologic, pathophysiological, pharmacological, and toxicological conditions.

Dr. Nathan Cherrington received postdoctoral training from Dr. Klaassen, after receiving a Ph.D. degree from North Carolina State University. Currently, he is a professor of pharmacology and toxicology and Associate Dean of Research at the College of Pharmacy of the University of Arizona. In this special section, Dr. Cherrington's group contributes a review article on the utility of exogenous drug disposition as a diagnostic biomarker strategy for nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) (Marie et al., 2022). This article provides an overview of noninvasive techniques, such as imaging, and panels of biomarkers of exogenous drug metabolites that are used to diagnose NAFLD and NASH along with a biopsy.

Dr. Cheryl Rockwell did postdoctoral training with Dr. Klaassen after she received a Ph.D. degree from Michigan State University. Currently, she is an associate professor of pharmacology and toxicology at Michigan State University. In this special section, her group contributes a review article on the intricate role of NRF2 in various inflammatory diseases, such as allergy and asthma. This article emphasizes the endogenous role of NRF2 in regulating immune cell function and in detoxifying xenobiotics that exacerbate these diseases (Rockwell et al., 2022).

Dr. Nichole Vansell received her Ph.D. degree with Dr. Klaassen. Currently, she is a senior scientist at Pfizer. She contributes a review article in this special section on mechanisms by which inducers of drug metabolizing enzymes alter homeostasis of thyroid hormones (Vansell 2022). The article emphasizes that the knowledge of inducible thyroid hormone transport into and out of liver, beyond induction of glucuronidation, should be considered and applied to screening and risk assessment paradigms when assessing an inducer's potential to alter thyroid homeostasis in nonclinical species and humans.

Collectively, these papers highlight the importance of bile acid homeostasis and a multitude of nuclear receptor signaling pathways in the regulation of drug metabolism and the translational potential for disease diagnosis or prevention. They also highlight the scientific contributions made by Dr. Curtis Klaassen and his trainees in the field of drug metabolism and disposition and related areas.

Xiao-bo Zhong and Yurong Lai
Minireviews Editors

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