

Special Section On Drug Metabolism in Liver Injury and Repair—Editorial

Received February 11, 2022; accepted March 3, 2022

This special section features articles by Dr. Huichang Bi, the recipient of the 2021 Richard Okita Early Career Award in Drug Metabolism and Disposition (the Okita Award), and her former mentors or collaborators. The liver is the most frequently injured abdominal organ following exposure to xenobiotic compounds, including drugs, while it is also an organ with capability to regenerate and undergo repair after injury. Numerous fundamental questions remain to be answered for understanding the impact of liver injury and repair on drug metabolism, including:

- (1) what molecular mechanisms are involved in liver injury and regeneration,
- (2) what key co-factors cause liver injury,
- (3) how susceptibility to liver injury can be caused by certain compounds and their metabolites,
- (4) how novel clinical biomarkers for indication of liver injury can be identified,
- (5) how novel strategies for the treatment of liver injury can be developed,
- (6) what consequence on liver's capability to metabolize drugs under liver injury condition can happen, and
- (7) what novel roles of epigenetics, such as long noncoding RNAs (lncRNAs), can be found in susceptibility of drug-induced liver injury (DILI).

In this special section of Drug Metabolism and Disposition (DMD), focused on “Drug Metabolism in Liver Injury and Repair,” Dr. Huichang Bi and the other contributors attempt to address some of these questions.

Dr. Bi obtained her Ph.D. degree under the mentorship of Dr. Min Huang at Sun Yat-sen University in Guangzhou, China, in 2007, and received postdoctoral training from Dr. Frank J. Gonzalez at the National Cancer Institute of National Institutes of Health (NIH), between 2011 and 2012. She started her faculty career at the Sun Yat-sen University School of Pharmaceutical Sciences and currently is a Professor and Dean of the School of Pharmaceutical Sciences at Southern Medical University, Guangzhou, China. She has published over 100 papers and 11 book chapters and has served as the primary mentor for over 40 graduate students and postdoctoral fellows. Dr. Bi is an active member of the American Society for Pharmacology and Experimental Therapeutics (ASPET) and a member of the DMD editorial advisory board. In 2018, Dr. Bi received the Asia Pacific New Investigator Award from the International Society for the Study of Xenobiotics (ISSX). At the 2021 ASPET Annual Meeting, Dr. Bi was awarded the Okita Award in recognition of her research excellence and contributions to the drug metabolism and pharmacokinetics (DMPK) field (Fig. 1).

Dr. Bi has had a longstanding interest in studying the metabolism of xenobiotics and endobiotics and their effects on diseases and clinical regimens, especially the drug-disease interactions mediated by nuclear receptors. Recently, she and her collaborators have made significant contributions to understanding nuclear receptor-mediated liver injury and regeneration, including novel mechanisms of pregnane X receptor (PXR), constitutive androstane receptor (CAR), and peroxisome proliferator-activated receptor alpha (PPAR α) involvement in promoting hepatomegaly and liver regeneration via interactions with yes-associated protein (YAP). Her findings provide new insights for understanding the mechanism of nuclear receptor-mediated liver enlargement and regeneration, the physiologic functions of these nuclear receptors, and potential for manipulation of liver size and liver regeneration (Jiang et al., 2019; Gao et al., 2021; Fan et al., 2022). In this special section, Dr. Bi contributes a comprehensive review on the nuclear receptor-mediated hepatomegaly and liver regeneration, including a perspective on nuclear receptors as therapeutic targets in the treatment of liver diseases (Zhao et al., 2022).

Four other review articles are included in this special section. Dr. Xiaochao Ma's group reviews the role of various contributing factors in DILI (Gu et al., 2022). Dr. Xiaochao Ma is a Professor of Toxicology at the School of Pharmacy of University of Pittsburgh. Multiple contributing factors are considered in their paper, including drug metabolizing enzymes, transporters, inflammation, age, gender, comorbidity, gut microbiota, and lifestyle. The underlying mechanisms of the involvement of these factors in DILI are discussed along with various capabilities to predict and prevent DILI.

Dr. Jiang Zheng's group provides a review on the metabolic activation and hepatotoxicity of furan-containing compounds (Tian et al., 2022). Dr. Zheng is a Professor of Toxicology at Shenyang Pharmaceutical University and Guizhou Medical University. His article explores the relationship between the metabolic activation and hepatotoxicity of furan-containing compounds. The pharmacological activities as well as concrete evidence of their ability to cause liver injuries are described, and the potential toxic mechanisms are discussed.

ABBREVIATIONS: ASPET, American Society for Pharmacology and Experimental Therapeutics; DMD, Drug Metabolism and Disposition; DILI, drug-induced liver injury; lncRNA, long noncoding RNA.

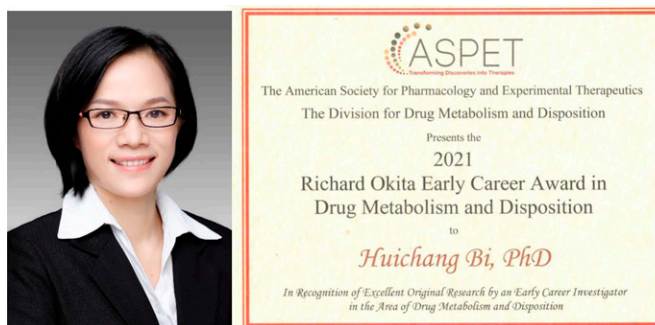


Fig. 1. Dr. Huichang Bi was the recipient of the Richard Okita Early Career Award in Drug Metabolism and Disposition, awarded by the Drug Metabolism and Disposition Division of ASPET, in 2021. Photos are reproduced with permission from Dr. Huichang Bi.

Dr. Min Huang's group summarizes recent advances in novel clinical biomarkers for DILI prediction, diagnosis, and prognosis, highlighting the limitations or challenges involved in biomarker discovery and their clinical translation (Chen et al., 2022).

Dr. Frank J. Gonzalez's group reviews the utility of Withaferin A (WA) in the treatment of acute and chronic liver injury, systematic inflammation, and liver cancer. They summarize the pharmacokinetic behavior, toxicity, and metabolism of WA, as well as pharmacological potentials of other extracts from *W. Somnifera*, and highlight the current progress and future opportunities from pharmacokinetic insights (Xia et al., 2022).

Two original research articles are also included in this special section. Bao and coworkers studied cytochrome P450 (CYP)-mediated drug metabolism during liver repair and regeneration after acetaminophen-induced liver injury (AILI) (Bao et al., 2022). The authors report a low-CYP expression window after AILI, which can decrease drug metabolism and impact on drug efficacy and adverse drug reactions during liver regeneration. Wang and coworkers explored the role of lncRNAs hepatocyte nuclear factor 4A antisense RNA 1 (HNF4A-AS1) and hepatocyte nuclear factor 1A antisense RNA 1 (HNF1A-AS1) in ritonavir (RTV)-induced cytotoxicity in hepatoma cells (Wang et al., 2022). The authors report that HNF4A-AS1 and HNF1A-AS1 modulate RTV-induced hepatotoxicity by regulating CYP3A4 expression, primarily by affecting the binding of PXR and altering histone modification status in the *CYP3A4* promoter.

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References

- Bao Y, Phan M, Zhu J, Ma X, Manautou JE, and Zhong XB (2022) Alterations of Cytochrome P450-Mediated Drug Metabolism during Liver Repair and Regeneration after Acetaminophen-Induced Liver Injury in Mice. *Drug Metab Dispos* **50**:694–703.
- Chen Y, Guan S, Guan Y, Tang S, Zhou Y, Wang X, Bi H, and Huang M (2022) Novel Clinical Biomarkers for Drug-Induced Liver Injury. *Drug Metab Dispos* **50**:671–684.
- Fan S, Gao Y, Qu A, Jiang Y, Li H, Xie G, Yao X, Yang X, Zhu S, Yagai T et al. (2022) YAP-TEAD mediates PPAR α -induced hepatomegaly and liver regeneration in mice. *Hepatology* **75**:74–88.
- Gao Y, Fan S, Li H, Jiang Y, Yao X, Zhu S, Yang X, Wang R, Tian J, Gonzalez FJ, et al. (2021) Constitutive androstane receptor induced-hepatomegaly and liver regeneration is partially *via* yes-associated protein activation. *Acta Pharma Sin B* **11**:727–737.
- Gu R, Liang A, Liao G, To I, Shehu A, and Ma X (2022) Roles of Cofactors in Drug-Induced Liver Injury: Drug Metabolism and Beyond. *Drug Metab Dispos* **50**:646–654.
- Jiang Y, Feng D, Ma X, Fan S, Gao Y, Fu K, Wang Y, Sun J, Yao X, Liu C, et al. (2019) Pregnane X Receptor Regulates Liver Size and Liver Cell Fate by Yes-Associated Protein Activation in Mice. *Hepatology*. **69**:343–358.
- Tian M, Peng Y, and Zheng J (2022) Metabolic Activation and Hepatotoxicity of Furan-Containing Compounds. *Drug Metab Dispos* **50**:655–670.
- Wang X, Yu Y, Wang P, Yang K, Wang YT, Yan L, Zhong XB, and Zhang L (2021) Long Noncoding RNAs Hepatocyte Nuclear Factor 4A Antisense RNA 1 and Hepatocyte Nuclear Factor 1A Antisense RNA 1 Are Involved in Ritonavir-Induced Cytotoxicity in Hepatoma Cells. *Drug Metab Dispos* **50**:704–715.
- Xia Y, Yan M, Wang P, Hamada K, Yan N, Hao H, Gonzalez FJ, and Yan T (2022) Withaferin A in the Treatment of Liver Diseases: Progress and Pharmacokinetic Insights. *Drug Metab Dispos* **50**:685–693.
- Zhao P, Fan S, Gao Y, Huang M, and Bi H (2022) Nuclear Receptor-Mediated Hepatomegaly and Liver Regeneration: An Update. *Drug Metab Dispos* **50**:636–645.

[dx.doi.org/10.1124/dmd.122.000869](https://doi.org/10.1124/dmd.122.000869).