50th Anniversary Celebration Collection

Special Section on New and Emerging Areas and Technologies in Drug Metabolism and Disposition, Part I—Editorial

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“Special Section on New and Emerging Areas and Technologies in Drug Metabolism and Disposition, Part I” presents nine articles mainly contributed by the current Editorial Advisory Board (EAB) members of Drug Metabolism and Disposition (DMD) and additional notable contributors to the field (Table 1). This special section is a part of the 50th Anniversary Celebration Collection. More articles will be published in Part II in the near future. These articles offer the latest insights into novel and emerging advancements in the realm of drug metabolism and disposition research.

Liquid-liquid phase separation (LLPS) is a phenomenon in the cells to define different functional compartments in membraneless organelles. RNAs and proteins are the key elements to establish LLPS in some cellular organelles, such as NEAT1_2 [a long noncoding RNA (lncRNA)] and DAZ-associated protein 1 (DAZAP1) in paraspeckles in a nucleus. An article in this special section titled “NEAT1_2 and DAZAP1, paraspeckle components, interact with PXR to negatively regulate CYP3A4 induction” (Mitamura et al., 2023), contributed by EAB member Dr. Miki Nakajima, illustrates for the first time the involvement of LLPS in pregnane X receptor (PXR)-mediated induction of cytochrome P450 3A4 (CYP3A4) expression. Dr. Nakajima is a Professor at the Faculty of Pharmaceutical Sciences from Kanazawa University and has been an EAB member of DMD since 2022. She is also a recognized Most Prolific DMD Author (Ding, 2023). Her group demonstrated that knockdown of the paraspeckle components of lncRNAs NEAT1_2 and DAZAP1 protein increases CYP3A4 induction by rifampicin in HepG2 cells. They further revealed that PXR interacts with paraspeckle members of NEAT1_2 and DAZAP1 in the absence of a PXR ligand and that the interactions between PXR and the paraspeckle components are blocked in the presence of a PXR ligand rifampicin, resulting in more PXR available for CYP3A4 induction. This finding provides a novel concept that paraspeckles formed by LLPS potentially affect drug metabolism via negative regulation of PXR functions.

A minireview article titled “Novel approaches to characterize individual drug metabolism and advance precision medicine” (Jackson et al., 2023), contributed by EAB member Dr. Klarissa D. Jackson, provides an overview of recent advances in technologies to characterize individual drug metabolism phenotypes in clinical settings. Dr. Jackson is an Assistant Professor from the Eshelman School of Pharmacy at the University of North Carolina and has been an EAB member of DMD since 2022. She recently received the Richard Okita Early Career Award in Drug Metabolism and Disposition in 2023. Her article concludes with perspectives on the future development of a liquid biopsy-informed physiologically based pharmacokinetic (PBPK) methodology for patient characterization and precision dosing in the clinical setting.

Optical substrates for cytochrome P450 (P450) enzymes have emerged as powerful tools for constructing fluorescence-based high-throughput assays for screening P450-mediated drug-drug interactions (DDIs). A minireview article titled “Fluorescence-based high-throughput assays for investigating P450-mediated drug-drug interactions” (He et al., 2023) is contributed by EAB member Dr. Guangbo Ge, who is a Professor at the Shanghai University of Traditional Chinese Medicine and has been a DMD EAB member since 2022. His article covers the advanced knowledge and challenges in developing highly specific optical substrates for sensing human P450 enzymes and their applications in constructing fluorescence-based high-throughput assays for investigating P450-mediated DDIs.

Mass spectrometry (MS)-based in situ imaging systems are highly responsive analytical approaches with target-free and high-throughput features to provide qualitative and quantitative analyses of biologic molecules for their distributions in...
Women with the preeclampsia (PE) condition during pregnancy may have different capabilities for drug absorption, distribution, metabolism, and excretion (ADME) compared with women without PE. Therefore, the characterization of ADME of prescription drugs in PE women is critical for optimizing efficacy and reducing toxicity. However, due to ethical concerns over research involving pregnant women, such ADME studies must first be done in a preclinical model. A comprehensive characterization of the preclinical model of the disease is thus necessary to determine its validity to the human condition. A research article in this special section titled “Use of traditional and proteomic methods in the assessment of a preclinical model of preeclampsia” (Dai et al., 2023) is contributed by EAB member Dr. Micheline Piquette-Miller, who is a Professor of Clinical Pharmacy at University of Toronto and has served on the DMD EAB since 2022. By applying traditional and proteomic methods of model characterization, Dr. Piquette-Miller’s laboratory identified numerous phenotypic similarities between an immunologic rat model of PE and human disease. The alignment with human pathophysiological changes allows more confident use of this preclinical model to study ADME of drugs under the PE condition.
Through computational methods, the high-resolution experimental structures of drug transporters may provide functional predictions of drug disposition, clinical efficacy, and toxicity. A review article with the title “The important role of transporter structures in drug disposition, efficacy, and toxicity” (Fu et al., 2023), contributed by EAB member Dr. Su Zeng and his collaborator Dr. Feng Zhu, collects structure information on the ATP-binding cassette (ABC) and solute carrier (SLC) transporters and describes the application of computational methods for structure prediction. Dr. Zeng is a Professor in the College of Pharmaceutical Sciences at Zhejiang University and has served on the DMD EAB since 2015. Dr. Zhu is also a Professor in the College of Pharmaceutical Sciences at Zhejiang University. Using P-glycoprotein and serotonin transporter as examples, they showed the pivotal role of transporter structures in drug selectivity, the molecular mechanisms of DDIs through competition on the transporters, and functional differences of transporters caused by genetic polymorphisms.

Antibody-drug conjugates (ADCs) are a class of biopharmaceutical drugs designed as a targeted therapy for treating cancer. ADCs conjugate a chemotherapy drug to a monoclonal antibody via a linker. The antibody can specifically bind to a receptor expressed on the cancer cell surface to precisely deliver the chemotherapy drug to certain types of cancer without damaging healthy cells. Understanding ADME features of ADCs is critical for optimizing therapeutic efficacy and reducing toxicity. EAB member Dr. Jingkai Gu contributes a review article to this special section titled “Bioanalytical assays for pharmacokinetic and biodistribution study of antibody-drug conjugates” (Yin et al., 2023). Dr. Gu is a Professor at the Research Center for Drug Metabolism at Jilin University and has served on the DMD EAB since 2022. His article describes bioanalysis methods for the pharmacokinetic study of ADCs and discusses the advantages, disadvantages, and potential challenges of these bioanalytical assays. The report provides valuable reference information for ADME studies in developing ADC drugs.

With the nine articles published, “Special Section on New and Emerging Areas and Technologies in Drug Metabolism and Disposition, Part I” provides advanced knowledge in several exciting areas in drug metabolism and disposition. More articles will be included in Part II of the special section.