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50th Anniversary Celebration Collection

Special Section on Perspectives on Drug Metabolism and Disposition, Part I—Editorial

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The "Perspectives on Drug Metabolism and Disposition" special section features articles contributed by the current associate editors of Drug Metabolism and Disposition (DMD) to the 50th Anniversary Celebration Collection (Ding, 2023). The Collection already includes a number of articles (Ding, 2023; Gillam and Kramlinger, 2023; Guengerich, 2023; Isin, 2023; McColl et al., 2023; Morgan et al., 2023; Roberts et al., 2023; Yamazaki and Shimizu, 2023), with many more to come.

The special section of Perspectives on Drug Metabolism and Disposition is divided into two parts. In Part I, five of our esteemed colleagues provide their perspectives on specific subjects in their areas of expertise.

Human absorption, distribution, metabolism, and excretion (ADME) studies hold immense significance as they provide a comprehensive and quantitative understanding of the overall disposition of a drug candidate in humans. A review article authored by Dr. R. Scott Obach, one of the *Most Prolific Authors in DMD* (Ding, 2023), and his colleagues at Pfizer, Inc., entitled "Human absorption, distribution, metabolism, and excretion studies: origins, innovations, and importance" (Cerny et al., 2023), offers a historical perspective on the origins of ADME studies and their advancements that have taken place since the pioneering work of George de Hevesy, who earned the 1943 Nobel Prize in Chemistry. The paper highlights the fact that DMD has served as an essential platform for the dissemination of ADME study findings for the past 5 decades. The article also delivers a comprehensive background on the progress of human ADME studies and technological advancements, describing the impact of technological and instrumental breakthroughs on the approaches used at different times for conducting human ADME studies and showcasing the ongoing debate concerning the significance of animal ADME studies versus a "human-first, human-only strategy."

Pollutant chemicals can interfere with the normal functions of hormones, which play a critical role in controlling liver xenobiotic-metabolizing enzymes, such as cytochromes P450s. Dr. David S. Riddick of the University of Toronto studies how hormones produced by the pituitary and adrenal glands affect an organism's sensitivity to the toxic effects of polycyclic aryl hydrocarbons by modulating the aryl hydrocarbon receptor (AhR) signaling pathway and the mechanisms by which AhR-activating chemicals disrupt endocrine pathways, resulting in down-regulated expression and function of hepatic P450s. In his review article "Fifty years of aryl hydrocarbon receptor research as reflected in the pages of drug metabolism and disposition" (Riddick, 2023), Dr. Riddick provides a decade-by-decade summary of significant historical discoveries in the AhR field and recognizes the numerous contributions made by publications featured in DMD. The article inspires present and future researchers in the AhR field by taking a historical journey through these landmark studies.

Dr. Xiao-bo Zhong and a colleague from the University of Connecticut reviewed the emergent topic of epigenetic regulation of gene expression in their article titled "Epigenetic mechanisms contribute to intraindividual variations of drug metabolism mediated by cytochrome P450 enzymes" (Jin and Zhong, 2023). Genetic polymorphisms primarily cause interindividual differences, whereas epigenetic mechanisms, including DNA methylation, histone modifications, microRNAs, and long noncoding RNAs contribute additionally to intraindividual variations. In this paper, Dr. Zhong and his colleague provide an in-depth analysis of the latest advancements in this area in the past decade and the contributions of various types of epigenetic modifications to intraindividual variations in cytochrome P450–mediated drug metabolism. The article highlights the role of epigenetic mechanisms in regulating drug metabolism within individuals, including the potential impact of epigenetic modifications on the expression of drug- metabolizing enzymes during development or by environmental exposures and drug treatments.

Dr. Aiming Yu of the University of California Davis is an expert on drug metabolism interested in noncoding RNAs, anticancer pharmacology, pharmacokinetics, pharmacodynamics, and experimental therapeutics. His laboratory has been exploring cutting-edge RNA bioengineering technologies for investigating the mechanisms by which microRNAs regulate cellular processes, including metabolism and the progression and metastasis of tumors, to create innovative therapies. The review article contributed by Dr. Yu and his colleague, titled "Recombinant Technologies Facilitate Drug Metabolism, Pharmacokinetics, and General Biomedical Research," summarizes the various recombinant DNA technologies that enable researchers to produce almost any ADME gene product for functional and structural analyses to study drug metabolism and

pharmacokinetics (Cronin and Yu, 2023). The article presents an overview of the latest RNA technologies and the potential utilities of bioengineered RNA agents in investigating ADME gene regulation and other areas of biomedical research.

Finally, Dr. Nina Isoherranen and colleagues at the University of Washington discuss the "Impact of intracellular lipid binding proteins (iLBPs) on endogenous and xenobiotic ligand metabolism and disposition" (Yabut and Isoherranen, 2023). They performed an in-depth review of various aspects of iLBPs related to these proteins' potential contributions to xenobiotic distribution and metabolism, including tissue-specific expression and functions, ligand binding characteristics, known endogenous and xenobiotic ligands, and mechanisms of delivering ligands to membranes and enzymes. They also describe the methods for measuring ligand binding and available evidence supporting the potential importance of iLBPs in modulating xenobiotic disposition. The review pays particular attention to fatty acid binding proteins, which constitute the bulk of iLBPs and can bind many types of drugs, such as nonsteroidal anti-inflammatory drugs, cannabinoids, benzodiazepines, antinociceptives, and peroxisome proliferators. It suggests the need to assess drug binding to the fatty acid binding proteins more regularly as is done for serum albumin binding.

DMD covers a broad range of topics as listed in our Instructions for Authors (https://dmd.aspetjournals.org/content/ifora#Scope_of_Submited_Manuscripts). The articles in this special section highlight only a few topics and historical perspectives in the drug metabolism and disposition field. Additional topics will be discussed in Part II and other future special sections.

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