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## EDITORIAL

# Advanced knowledge in drug metabolism and pharmacokinetics



Drug metabolism and transport in human organs, such as in the liver, intestine, and kidney, control the concentrations of a drug and its metabolites in the circulating system and target organs in a certain period of time following drug administration. The pharmacokinetic properties will consequently determine therapeutic efficacy and influence toxicological effects. Changes of drug metabolism and pharmacokinetics may result in significant inter-individual variations in therapeutic efficacy and adverse drug reactions. Therefore, understanding drug metabolism and pharmacokinetic properties is essential for drug development and clinical therapy. Growing researches in these areas also promote the development of novel approaches to implementation of personalized medicine or precision medicine. This special issue consists of a set of original research and review articles providing recently-gained information in these areas. As the guest Editors, we would like to appreciate the journal for providing us the opportunity to share the information and thank all authors for their contributions.

Cytochrome P450 (CYP or P450) enzymes are the major superfamily of phase I drug-metabolizing enzymes. Extensive studies have demonstrated the impact of hepatic P450 functions and regulation on drug metabolism and responses. However, intestinal P450-mediated drug metabolism is an important factor dictating first-pass metabolism and oral bioavailability. Fang Xie and colleagues provide an updated review on the role of intestinal P450 enzymes in drug disposition (see a story for the front cover)<sup>1</sup>. The utility of genetically engineered mouse models, which target the P450-reductase (CPR) on specific tissues, in defining the contribution of intestinal and hepatic P450s to drug metabolism and pharmacokinetics is also discussed. CYP2B6 is one isoform among P450 superfamily and it metabolizes 2%–10% of clinically-used drugs. William Hedrich and colleagues present an overview on key players in the regulation of CYP2B6 expression and functions and highlight recent advanced knowledge in CYP2B6-mediated drug–drug interactions<sup>2</sup>. Transporters are another superfamily of proteins involved in drug absorption, distribution, and elimination. In particular, renal drug transporters play an important role in secretion and reabsorption of drugs in the kidney. Jia Yin and Joanne Wang give a comprehensive review on the functional

characteristics of major human renal drug transporters and their involvement in clinically significant pharmacokinetic drug–drug interactions (see a story for the back cover)<sup>3</sup>.

Several key transcription factors, including pregnane X receptor (PXR), constitutive androstane receptor (CAR), farnesoid X receptor (FXR), hepatocyte nuclear factor 4 alpha (HNF4 $\alpha$ ), and estrogen receptor (ER), have been demonstrated to play important roles in the regulation of gene expression of drug-metabolizing enzymes and transporters. Several research and review articles have focused on novel aspects of these transcription factors in the regulation of drug metabolism and transport gene expression. Jiong Yan and Wen Xie describe a historical overview on the discovery of PXR and CAR as xenobiotic receptors<sup>4</sup>. Trent Brewer and Taosheng Chen discuss several PXR protein variants and their impact on drug metabolism and therapeutic responses<sup>5</sup>. Shinhee Park and colleagues characterize gene expression of CAR-targeted drug-metabolizing enzymes and transporters in mouse intestine<sup>6</sup>. Hong Lu gives a comprehensive review on HNF4 $\alpha$ -controlled gene expression and crosstalks of HNF4 $\alpha$  with diverse extracellular and intracellular signaling pathways in the modulation of hepatic drug metabolism and lipid homeostasis<sup>7</sup>. Yan Zhu and colleagues provide a review on the critical roles of FXR in the control of bile acid homeostasis and illustrate the molecular mechanisms behind dysregulation of bile acids in promoting liver injury and nonalcoholic fatty liver disease<sup>8</sup>. Lai Peng and colleagues determine the role of FXR in establishment of ontogeny of phase I drug-metabolizing enzyme gene expression in mouse liver<sup>9</sup>. Sung-joon Cho and colleagues demonstrate that upregulation of UGT1A9 gene expression by estradiol is a transcriptional response to the activation of ER $\alpha$  receptor<sup>10</sup>.

Pharmacokinetics/pharmacodynamics (PK/PD) modeling and simulation offer quantitative understanding of drug exposure and response, guide the selection of dose and dose regimen, and predict interindividual variability towards precision medicine. Xiaomei Zhuang and Chuang Lu provide an overview on the concept and methodology of physiologically based pharmacokinetic (PBPK) modeling<sup>11</sup>. Case studies are presented to illustrate how PBPK modeling and simulation may benefit drug discovery

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and development at various stages. Wenli Liu and colleagues use nimodipine as a model drug to demonstrate the potential effects of age and polymorphic form on pharmacokinetics in rats<sup>12</sup>. Xi-ling Jiang and colleagues describe the development of a new mechanism-based PK/PD model to characterize the thermoregulatory effects of serotonergic drugs in mouse models, which may serve as a new framework for the investigation of thermoregulatory or other neuropharmacological effects of serotonergic agents<sup>13</sup>.

Distribution of a drug to target tissues is essential to achieve therapeutic effects, while production of reactive metabolites may provoke xenobiotics-induced tissue and organ damage. Hong Shen and colleagues demonstrate tissue distribution and tumor uptake of a folate receptor-targeted, anticancer agent epothilone folate conjugate in xenograft tumor mouse models following systemic administration<sup>14</sup>. Pengcheng Wang and colleagues provide an overview on the metabolic pathways of isoniazid and their possible associations with isoniazid-induced liver injury<sup>15</sup>. In addition, Jonathan Choiniere and Li Wang provide a mini-review on the impact of environmental arsenic on gut microbe and possible link to arsenic-induced carcinogenesis<sup>16</sup>.

We hope this special issue would serve as a valuable information resource for our readers to gain more knowledge in the fields of drug metabolism and pharmacokinetics.

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