Enzyme- and Transporter-Based Drug–Drug Interactions
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Progress and Future Challenges
Preface

Germination of the thought of “Enzyme- and Transporter-Based Drug–Drug Interactions: Progress and Future Challenges” proceedings came about as part of the annual meeting of The American Association of Pharmaceutical Scientists (AAPS) that was held in San Diego in November 2007. The attendance of the workshop by more than 250 pharmaceutical scientists reflected the increased interest in the area of drug–drug interactions (DDIs), the greater focus of pharmaceutical industry, academia, and regulatory agencies, and the rapid pace of growth in knowledge. The aims of the workshop were to address the progress made in quantitatively predicting enzyme- and transporter-based DDIs as well as highlight areas where such predictions are poor or areas that remain challenging for the future. Because of the serious clinical implications, initiatives have arisen from the FDA (http://www.fda.gov/cber/gdlns/interactstud.htm) to highlight the importance of enzyme- and transporter-based DDIs.

During the past 10–15 years, we have come to realize that transporters, in addition to enzymes, play a vital role in drug elimination. Such insight has been possible because of the continued growth in PK-ADME (pharmacokinetics-absorption-distribution-metabolism-excretion) knowledge, fueled by further advances in molecular biology, greater availability of human tissues, and the development of additional and sophisticated model systems as well as sensitive assay methods for the study of drug metabolism in vitro and in vivo. This has sparked an in-depth probing into mechanisms surrounding DDIs, resulting from ligand-induced changes in nuclear receptors, as well as alterations in transporter and enzyme expression and function. Despite such advances, the in vitro and in vivo study of drug interactions and the integration of various data sets remain challenging. Therefore, it has become apparent that a proceeding that serves to encapsulate current strategies, approaches, methods, and applications is necessary.

As editors, we have assembled a number of opinion leaders and asked them to contribute chapters surrounding these issues. Many of them are the original workshop speakers whereas others had been selected specially to contribute on topics related to basic and applied information that had not been covered in other reference texts on DDIs. The resulting volume, entitled *Enzyme- and Transporter-Based Drug–Drug Interactions: Progress and Future Challenges,* comprises of four sections. Twenty-eight chapters dedicated to various topics and perspectives related to enzyme and transporter-based drug interactions are included. The chapters cover a wide range of subjects, including the use of model systems, the study of interactions through in vitro and in vivo methods, and the integration of data from various sources to improve prediction of DDIs.

The aim of this proceeding is to provide a comprehensive overview of the current state of knowledge in the field of enzyme- and transporter-based DDIs, along with future directions and challenges. It is hoped that this volume will be a valuable resource for researchers, practitioners, and regulatory authorities involved in the study and prediction of DDIs.
to the subject of metabolic and transporter-based drug–drug interactions are presented. Section I covers scientific issues and concepts that dwell on the fundamental understanding of transporters and enzymes, their function and regulation by nuclear receptors, and how these work in unison or in competition, in first-pass absorption, transport, and metabolism. Since the first mandate is an understanding of what kinds of transporters, enzymes and eliminating organs are involved in the handling of the drug in terms of deciphering the mechanisms involved in DDI, various organs including the kidney are discussed. Kinetic concepts describing clearance mechanisms and areas under the curve of not only drug but also metabolite have also been introduced. Section II pertains to methodology for the study of DDI. Due to the cost requirement in mounting in vitro vs. in vivo studies, DDI studies are often explored in vitro and the tools, the extrapolation of data in vitro to in vivo from animal to man, together with information retrieval from web data basis for transporters (www.TpResearch.com) and enzymes (www.DrugInteractionInfo.org) as well as modeling and simulations have been addressed. Section III covers the various topics that impact DDIs and spans competitive to allosteric- and mechanism-based inhibition, inductive, time-dependent alteration in drug elimination rates, inhibition of Phase II pathways, changes in volume and first-pass metabolism, and the final integration of data. Lastly, Section IV describes regulatory aspects and future developments, stressing the use of clearance concepts, PBPK models, and modeling and simulations as well as future challenges that would be faced. It is our hope that the proceedings bring about an improved appreciation of the impact of DDI and a deeper understanding of “where we had been and where we are going.”

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