ASCPT Science at Sunrise Session, March 7, 2015 (7:30-9:00 AM)

Session Title: **New Insights and Novel Biomarkers for Predicting Transporter-Mediated Drug-Drug Interactions: A Multi-sector Perspective**

Session co-Chairs:
Kathleen Hillgren, Ph.D., Investigational Drug Disposition, Lilly Research Laboratories.
Sook Wah Yee, Ph.D., University of California San Francisco, USA.

Learning Objectives:
The participants will be able to:
1. Discuss and provide examples of drug metabolites that cause drug-drug interactions and toxicities.
2. Describe the design of clinical studies to identify and to validate transporters biomarkers and list two challenges for using transporter biomarkers as part of the drug development process.
3. Describe new transporters in regulatory decision trees for transporter-mediated drug-drug interactions (DDI) and describe creatinine as a biomarker for renal drug interactions.

Speakers and Brief Highlights of the Presentations:

Maciej Zamek-Gliszczynski, Ph.D., GlaxoSmithKline, plc.
Drug Metabolites and Transporters: Perspective and Issues for drug development

Drug metabolites are generally polar and have low permeability across membrane, hence it is less likely to interact with cytochrome P450 but more likely to interact with transporters. As a result, membrane transporters could play important role in drug metabolite disposition, and interaction with transporter may alter drug efficacy and safety. In this session, Dr. Zamek-Gliszczynski will present case studies that suggest drug metabolites can alter efficacy (e.g. mycophenolic acid), toxicity (e.g. irinotecan) and/or drug-drug interaction profile (e.g. gemfibrozil) due to metabolite-transporter interactions. Overview of novel approaches in experimental and modeling, such as MALDI-IMS and PBPK tools will be discussed. Finally, recommendations for drug development to establish prediction of pharmacodynamics and toxicodynamic consequences of metabolite-transporter interaction will be discussed.

Kathy Giacomini, Ph.D., University of California, San Francisco
Discovery of Endogenous Biomarkers for Transporters

Endogenous biomarkers for drug metabolism have been well-described and can be used to assess the effects of new drugs on drug metabolism. For example, plasma levels endogenous substrates of CYP3A4 can be measured in the presence of new drugs to determine if the new drugs inhibit or induce the enzyme. In contrast, few biomarkers for transporters that function in the absorption and disposition of drugs have been described. In this session, Dr. Giacomini will describe various approaches including metabolomic, genomic, and clinical drug interaction studies for discovering endogenous biomarkers of transporters. She will specifically focus on discovery of endogenous biomarkers for the organic cation transporter, OCT1 and the multi-drug and toxin extrusion protein, MATE1. Problems with current biomarkers will be described along with criteria for guiding the selection of robust biomarkers that can be used to accurately predict transporter mediated drug-drug interactions. Finally, future directions for the discovery, validation and regulatory acceptance of biomarkers for membrane transporters will be presented.

Lei Zhang, Ph.D., Center for Drug Evaluation and Research, U.S. Food and Drug Administration
When should in vivo transporter-mediated drug-drug interaction studies be conducted? A regulatory perspective

Clinically relevant interactions mediated by transporters are of increasing interest in drug development. Research in this emerging area has revealed that drug transporters, acting alone or in concert with drug metabolizing enzymes, can play an important role in modulating drug absorption, distribution, metabolism and excretion, thus affect the pharmacokinetics and/or pharmacodynamics of a drug. The International Transporter Consortium (ITC) published whitepapers in 2010 and 2013 to guide clinical studies on

transporter-mediated drug-drug interactions (DDIs). Drug interaction guidances from various regulatory agencies include updated recommendations in addressing transporter-mediated drug interactions to help guide drug development. Dr. Zhang will provide an overview of factors to be considered on when to evaluate transporter-based interactions for major transporters including in vitro assays and possible criteria that may be used to guide decisions. The consequence of the interaction mediated by transporters may not always be apparent if an in vivo human DDI study only measures systemic exposure. However, the understanding of whether the drugs is a substrate or inhibitor of key transporters may help understand the underlying clinical consequences, such as increased toxicity signal or altered efficacy markers due to altered tissue distribution of a substrate drug. Recent review examples will be provided including increase in serum creatinine, an endogenous marker, as a possible renal transporter interaction indicator, and the utility and limitations of physiologically-based pharmacokinetic (PBPK) modeling in the evaluation of transporter-medicated drug interactions.

Figure 1. Key transporters interacting with drug metabolites in the intestine (GI), liver and kidney (Proximal tubule, PT) (Ref 1).

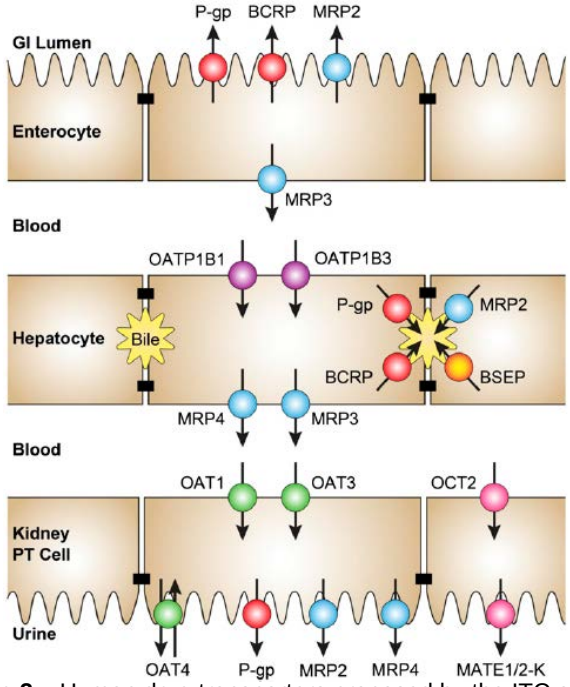
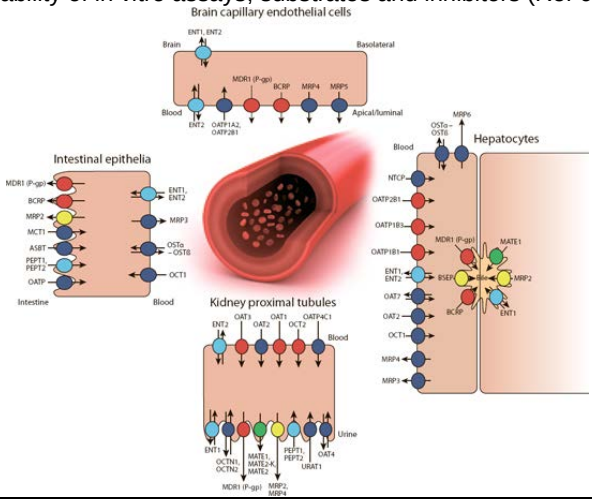


Figure 2. . Human drug transporters proposed by the ITC as being important for evaluation during drug development. Transporters were highlighted on the basis of evidence of clinical drug interactions and relevance to toxicity or efficacy, as well as availability of in vitro assays, substrates and inhibitors (Ref 6).



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