

Third Workshop on Membrane Transporters in Drug Development

Hosted by the International Transporter Consortium (ITC)

March 13-14, 2017

Omni Shoreham Hotel, Washington, DC

DAY 1 | MONDAY, MARCH 13, 2017

8:15 – 8:30 am **Welcome and Opening Remarks**
Kathy Giacomini, University of California San Francisco

Session 1: Membrane Transporters in Human Health and Pathobiology: From Biomarkers to Therapy

Moderators: Kim Brouwer (University of North Carolina, Chapel Hill) and Joseph Polli (GlaxoSmithKline)

8:30 – 9:00 am **Renal transporters, kidney disease and toxicity**
Jonathan Himmelfarb, University of Washington

9:00 – 9:30 am **Hepatic phospholipid and bile acid transport deficiencies: therapeutic/clinical implications**
Ronald Oude Elferink, Academic Medical Center, Amsterdam

9:30 – 10:00 am **Gout and uric acid; from disease to transporters to therapy**
Jeffrey N. Miner, Ardea Biosciences

10:00 – 10:30 am **Break**

Session 2: Imaging and Pharmacokinetics of Intracellular Distribution

Moderators: Shiew-Mei Huang (U.S. Food and Drug Administration) and Ken Korzekwa (Temple University)

10:30 – 11:00 am **Modeling intracellular concentrations with in vitro imaging and liver perfusion studies**
Ken Korzekwa, Temple University School of Pharmacy

11:00 – 11:30 am **Imaging Studies with the Transporter Probe ^{99m}Tc-Mebrofenin Reveal Altered Hepatic Exposure in Patients with Non-Alcoholic Steatohepatitis (NASH)**
Kim Brouwer, University of North Carolina, Chapel Hill

11:30 – 12:00 pm **Is prediction of tissue exposure from in vitro data using PBPK modeling possible? Confirmation by PET imaging to study the clinical disposition of membrane transporter substrates**
Yuichi Sugiyama, RIKEN

12:00 – 1:00 pm **Lunch and Poster Session**

Session 3: Recent and Emerging Transporters

Moderators: Maciej Zamek-Glisczynski (GlaxoSmithKline) and Richard Kim (University of Western Ontario)

- 1:00 – 1:30 pm **New developments in renal drug transport**
Adrian Ray, Gilead Sciences
- 1:30 – 2:00 pm **OATP2B1: in vitro, proteomic, and clinical PK relevance in GI and liver**
Jashvant Unadkat, University of Washington
- 2:00 – 2:30 pm **Emerging importance of nutrient transporter-mediated DDIs**
Yan Zhang, Incyte
- 2:30 – 3:00 pm **Break**
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Session 4: Modeling of Transporters from Molecular Mechanisms to PBPK

Moderators: Aleksandra Galetin (University of Manchester) and Pär Matsson (Uppsala University)

- 3:00 – 3:30 pm **Inhibitor Discovery for the Human GLUT1 from Homology Modelling and Virtual Screening**
Avner Schlessinger, Mount Sinai School of Medicine
- 3:30 – 4:00 pm **Computational modelling to predict the functions and impact of drug transporters**
Pär Matsson, Uppsala University
- 4:00 – 4:30 pm **PBPK modelling of renal impairment – what is missing?**
Aleksandra Galetin, University of Manchester
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- 4:30 – 5:30 pm **Breakout Sessions for Whitepapers**
- 4:30 – 7:00 pm **Poster Session and Reception**
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DAY 2 | TUESDAY, MARCH 14, 2017

7:15 – 8:15 am **Breakout Sessions for Whitepapers**

Session 5: Transporter Genomics: Genomewide and Massively Parallel Sequencing Studies

Moderators: Kathy Giacomini (University of California San Francisco) and Mikko Niemi (University of Helsinki)

8:30 – 9:00 am **Massively parallel sequencing of drug transporters - SLCO1B1 and beyond**
Mikko Niemi, University of Helsinki

9:00 – 9:30 am **Genomewide Studies Reveal Transporters as Determinants of Drug Response**
Kathy Giacomini, University of California San Francisco

9:30 – 10:00 am **Na⁺/citrate transporter [SLC13A5] variants in epilepsy and developmental delay**
Ana M. Pajor, University of California San Diego

10:00 – 10:30 am **Break**

Session 6: Biomarkers and Probes for Clinical Studies

Moderators: Lei Zhang (U.S. Food and Drug Administration) and Xiaoyan Chu (Merck)

10:30 – 11:00 am **Endogenous biomarkers for renal transporters**
Hiroyuki Kusuhara, University of Tokyo

11:00 – 11:30 am **Endogenous biomarkers for OATP1B: preclinical to clinical translation**
Yurong Lai, Gilead Sciences

11:30 – 12:00 pm **Pharmacokinetic Evaluation of a Drug Transporter Cocktail Consisting of Digoxin, Furosemide, Metformin, and Rosuvastatin**
Mitchell Taub, Boehringer Ingelheim

12:00 – 1:00 pm **Lunch and Poster Session**

Session 7: Regulatory Issues in Transporter Mediated Drug-Drug Interactions

Moderators: Donald Tweedie (Merck) and Yurong Lai (Gilead Sciences)

1:00 – 1:30 pm **FDA Perspective**
Lei Zhang, U.S. Food and Drug Administration

1:30 – 2:00 pm **A European Perspective**
Eva Gil Berglund, Medical Products Agency (Sweden)

2:00 – 2:15 pm **Case Study 1: Evaluation of Dabigatrin Etexilate as a Clinical Probe for P-gp Inhibition: Comparison with Digoxin**
Xiaoyan Chu, Merck

2:15 – 2:30 pm **Case Study 2: Induction: Drug Transporters versus Enzymes**
Justin Lutz, Gilead Sciences

2:30 – 2:45 pm	Case Study 3: Evaluation of Drug-Drug Interaction Potential Between Sacubitril/Valsartan (LCZ696) and Statins Using a Physiologically-Based Pharmacokinetic Model Imad Hanna, Novartis
2:45 – 3:00 pm	IVIVE of Transporter-Mediated Clinical Drug-Drug Interactions in Industry – An Update from the IQ Transporter Working Group Kari Morrissey, Genentech
3:00 – 4:00 pm	Panel Discussion with Academic, Industry and Regulatory Scientists Kathy Giacomini (UCSF), Joe Polli (GSK), Kathleen Hillgren (Eli Lilly), Shiew-Mei Huang (FDA), Eva Gil Berglund (EMA)
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4:00 – 4:15 pm	Closing Remarks and End of Workshop
4:15 – 5:15 pm	Open Forum to Provide Feedback to ITC
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Session Descriptions

Session 1 | Membrane Transporters in Human Health and Pathobiology: From Biomarkers to Therapy

Membrane transporters have a diversity of functions, from creating an efflux barrier against a drug to absorbing essential nutrients across membranes. Over the past decade, the interest in transporters within the ITC community has continued to grow from an initial focus on drug disposition and drug interactions to understanding the important role of membrane transporters in the disposition of nutrients and other endogenous compounds that impact human health and disease. This session will highlight recent work in the membrane transporter field from biomarkers to therapy related to kidney injury, hepatic dysfunction and chronic disease. The goal is to demonstrate the diverse cellular functions of membrane transporters as well as the critical importance of these processes to human health.

Session 2 | Imaging and Pharmacokinetics of Intracellular Distribution

Unbound intracellular concentrations are needed to predict the target and off-target activity of many drugs. Although the free drug hypothesis states that unbound intracellular and unbound extracellular drug concentrations will be equal at equilibrium, transporter activity can greatly alter intracellular concentrations. Direct measurement of unbound intracellular concentrations is difficult and modeling approaches have been used to convert measured *in vitro* and *in vivo* concentrations to estimates of intracellular concentrations in the presence of transporters. This session will discuss recent studies that use cellular and *in vivo* imaging, along with preclinical and clinical pharmacokinetic models to provide estimates of unbound intracellular drug concentrations.

Session 3 | Recent and Emerging Transporters

This session will highlight transporters of emerging clinical relevance to drug disposition and interactions. Emphasis will be placed on new mechanistic insight into intestinal, hepatic, and renal transport. Specifically, the recently-recognized importance of OAT2 in the kidney will be discussed. Importance of OATP2B1 as an intestinal and hepatic uptake pathway will be presented from a victim and perpetrator DDI perspective. Finally, nutrient transporter-mediated DDIs will be highlighted, with emphasis on intestinal THTR2 inhibition. The ultimate goal of the session is to stimulate discussion on whether there is sufficient clinical evidence to revise and/or expand ITC recommendations on transporter evaluation in drug development.

Session 4 | Modeling of Transporters from Molecular Mechanisms to PBPK

This session will discuss the use of computational modelling across multiple aspects of transporter science, ranging from the identification of novel transporter ligands, the uncovering of mechanisms of substrate recognition, to the delineation of transporter effects in clinical trial data. The presentations will discuss use of multiple sources of data in transporter modelling, including X-ray crystallographic protein structure data, ligand structural data, and *in vitro* and clinical data on substrate transport and transporter inhibition. Current state-of-the-art will be outlined, and future directions in transporter modelling will be suggested—from structure- and ligand-based approaches to drug–transporter interaction modelling, to physiologically-based pharmacokinetic modelling of transporter-mediated disposition in special populations

Session 5 | Transporter Genomics: Genomewide and Massively Parallel Sequencing Studies

Genomewide association studies have ushered in a new understanding of the role of common genetic polymorphisms in variation in drug disposition and response. From these studies, common variants in membrane transporters in the liver and kidney have been discovered to be major determinants of variation in pharmacokinetics and pharmacodynamics of many prescription drugs. In this session, we will present new information on the role of common genetic variants in transporters in the liver and kidney on drug disposition and response. That information will be presented in the context of other factors that contribute to pharmacokinetic and pharmacodynamics such as drug dose and patient demographic characteristics. New information on the effects of less common and rare variants in membrane transporters on drug disposition and response will be presented. Collectively, the session will provide the attendees with a rich overview of the effects of common and rare variants in hepatic and renal transporters on variation in drug disposition, toxicity and response.

Session 6 | Biomarkers and Probes for Clinical Studies

Transporter function could be modulated by multiple factors including genetic status, disease states or the presence of modulating drugs. Transporter-mediated drug interactions need to be evaluated as part of risk assessment during drug development. Decision criteria based on in vitro DDI assessments are recommended by the regulatory agencies to help determine the need for in vivo drug interaction evaluation. Endogenous biomarkers and probe substrates for various transporters are helpful in understanding the in vivo effect of perpetrator drugs on transporters. The selectivity profiles of endogenous biomarkers and probe substrates for various transporters need to be well characterized for study design and data interpretation. This session will highlight recent progress on identifying novel transporter biomarker probes for renal and hepatic transporters. Furthermore, the clinical evaluation of transporter cocktail probe substrates, which allows simultaneous assessment of a perpetrator drug's interaction potential on multiple transporters, will be discussed.

Session 7: Regulatory Issues in Transporter Mediated Drug-Drug Interactions

An updated DDI guidance is expected from the FDA. Drug-drug interaction (DDI) guidances from regulatory agencies (e.g., FDA, EMA and PMDA) have included recommendations on evaluating transporter-mediated DDIs in drug development. Regulatory scientists have considerable experience in applying their DDI guidances and in responding to submissions from sponsors in relation to transporters and drug development. This session offers an opportunity for direct interaction with regulatory scientists to hear their perspectives first hand. Additionally, there will be case studies presented by industry and academic scientists offering insights into issues associated with transporters in drug development. A panel discussion with key experts in the field of drug transporters from academia, industry and regulatory agencies will give the participants an opportunity to air their views, offer alternate perspectives and participate in an open discussion.