HT-ADME

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2019

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH AUDITORIUM
CAMBRIDGE, MA | APRIL 11

TRANSPORTER WORKSHOP

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ORGANIZERS' WELCOME

Welcome to the 2019 HT-ADME Transporter Workshop.

Our organizers have gathered another excellent group of speakers for this workshop. The program is arranged to incorporate extensive audience participation and discussion. We encourage attendees to take full advantage of the opportunity to engage in discussion in order to receive the maximum benefit from the HT-ADME experience.

Thank you for your participation.

ORGANIZING COMMITTEE

Dallas Bednarczyk, Novartis
Ayman El-Kattan, IFM Therapeutics
Maria Fitzgerald, Sanofi
Steven Louie, BioIVT
Hong Shen, BMS
Guangqing Xiao, Sunovion

HT-ADME 2019
TRANSPORTER WORKSHOP AGENDA

THURSDAY, APRIL 11

7:00 - 8:00 Registration & Breakfast

8:00 - 8:05 Conference Opening
Steven Louie, BioIVT

SESSION I: Emerging Transporter Targets in Pharma

8:05 - 8:10 **Session I Introduction**
Dallas Bednarczyk, Novartis & Steven Louie, BioIVT

8:10 - 8:40 **Transporters of Emerging Importance in Drug Development: Beyond the Guidance Document**
Brian Ogilvie, XenoTech

8:40 - 9:10 **Non-Alcoholic Fatty Liver Disease Phenotype in Regenerating Liver of Multidrug Resistance Associated Protein-4 (Mrp4) Deficient Mice**
Jose Manauton, University of Connecticut

9:10 - 9:40 **Quantitative Proteomics-Based REF vs. Activity-Based RAF Approaches to Predict Transporter-Mediated Drug Clearance**
Manthena Varma, Pfizer

9:40 - 10:00 Break

10:00 - 10:40 **PLENARY LECTURE**
Transporters, the Extended Clearance Concept and PBPK Modeling
Les Benet, UCSF School of Pharmacy

SESSION II: Quantitative Transporter Proteomics and PBPK Modeling/CNS Transporters

10:40 - 10:45 **Session II Introduction**
Maria Fitzgerald, Sanofi & Guangqing Xiao Takeda

10:45 - 11:15 **Vitamin D Enhances Folate Transport Across the Blood-Brain Barrier: Relevance to the Treatment of Cerebral Folate Deficienc**
Reina Bendayan, University of Toronto

11:15 - 11:45 **A Translational Strategy using in vitro Transporter Studies and in vivo NeuroPK to Predict Human Brain Penetration of P-gp and BCRP Substrates**
Bo Feng, Vertex

11:45 - 12:15 **IVIVE of Efflux Transport using Quantitative Proteomics Approach: Importance in Prediction of Enterohepatic Recirculation**
Bhagwat Prasad, University of Washington

12:15 - 1:15 Lunch

1:15 - 1:45 **VENDOR PRESENTATION**
An Integrated In Vitro Screen Using Sandwich-Culture Human Hepatocytes to Predict Cholestatic Hepatotoxicity
Jonathan Jackson, BioIVT

SESSION III: ITC White Papers

1:45 - 1:50 **Session III Introduction**
Hong Shen, BMS and Ayman El-Kattan, IFM Therapeutics

1:50 - 2:20 **ITC3 Recommendations on Bile Salt Export Pump (BSEP) Inhibition Investigations and an Industry Perspective**
Kunal Taskar, GSK, UK

2:20 - 2:50 **Utility of Clinically Relevant Probe Drugs and Endogenous Biomarkers for Transporter DDI Evaluation: Perspectives From the International Transporter Consortium**
Xiaoyan Chu, Merck

2:50 - 3:20 **Drug-Transporter Interactions and the Role of Transporters in Tissue and Cell Exposure – Views from Recent International Transporter Consortium White Papers**
Par Mattsson, Uppsala University, Sweden

3:20 - 3:35 Break

3:35 - 4:05 **Cutting Edge of Clinically-Relevant Transporter Probes and DDI Evaluation**
Maciej Zamek-Gliszczynski, GSK

4:05 - 4:35 **VENDOR PRESENTATION**
Accepting the Challenges of Regulatory Guidance
Zsuzsanna Gáborik, Solvo Biotechnology

4:35 - 5:15 **PLENARY LECTURE**
The Ins and Outs of An Overlooked Bile Acid Transporter, OSTα/β
Kim Brouwer, UNC Eshelman School of Pharmacy

5:15 - 6:15 **COCKTAIL RECEPTION**

ABSTRACTS

PLENARY LECTURE

Transporters, the Extended Clearance Concept and PBPK Modeling

Les Benet, UCSF School of Pharmacy

We recently derived the theoretical basis for the extended clearance model of organ elimination from first principle mass balance relationships following both oral and IV dosing. We point out a number of characteristics that have not been clearly specified and may be misinterpreted. The extended clearance concept is derived based on the well-stirred model. It is not appropriate to use alternate hepatic clearance models. The transport clearances in the equations are all intrinsic clearances, not total drug clearances. The systemic and protein binding terms reflect blood measurements, not plasma. We propose that calculations of AUCR may be a more useful approach to evaluate drug-drug and pharmacogenomic interactions, rather than characterizing rate limiting steps, and that the extent of transporter and metabolic interactions can be evaluated independent of knowledge of the β-factor. We emphasize the need to characterize the effect of transporter inhibition and induction on changes in volume of distribution, since volume terms affect half-life and other rate constants describing the concentration-time course. We make this observation with respect to PBPK models. Finally, we note that prediction of systemic and intrahepatic drug-drug interactions do not require knowledge of fraction unbound within the liver ($f_{u,H}$) or $K_{p,uu}$ for substrates/victims.

SESSION I

Non-Alcoholic Fatty Liver Disease Phenotype in Regenerating Liver of Multidrug Resistance Associated Protein-4 (Mrp4) Deficient Mice

Jose Manauton, University of Connecticut

Non-alcoholic fatty liver diseases (NAFLD) is a spectrum of disorders of varying severity beginning with simple steatosis that can progress to fibrosis. NAFLD is a growing concern in the US, since it affects 25% of general population and 75% of obese and diabetic individuals. Multidrug resistance-associated protein 4 (Mrp4, Abcc4) is a membrane bound protein involved in efflux of several endogenous molecules and xenobiotics. In both humans and rodents, hepatic Mrp4 exhibits low expression under basal condition, but is highly induced during liver damage caused by xenobiotics, and other disease conditions such as obesity, diabetes and fatty liver diseases. In our laboratory, we recently observed that the lack of Mrp4 results in hepatic steatosis in mice following partial hepatectomy (PH). Furthermore, lipidomics analysis shows that Mrp4-/- mice have increased hepatic di- and tri-glycerol lipid species following PH. Additionally, Mrp4-/- mice had increased adipose tissue weight and circulating plasma leptin levels. These are all factors known to play a significant role in the pathogenesis of hepatic steatosis. Research work to be discussed will highlight our efforts to define the molecular mechanisms by which the absence of Mrp4 alters hepatic lipid homeostasis. Preliminary data will also be presented addressing the role of Mrp4 in the adipose-liver lipid shunt.

Quantitative Proteomics-based REF vs. Activity-based RAF Approaches to Predict Transporter-mediated Drug Clearance and DDIs

Manthena V. Varma, Pfizer

Translation of transporter-mediated disposition is gaining considerable interest in medicine design as it certain now that the membrane transporters play a significant role in the ADME of small molecule drugs. Additionally, these proteins play a key role in regulating the tissue exposure of substrate drugs. Several in vitro tools are available to characterize transport mechanisms and estimate kinetic parameters (eg. cell cultures, vesicles, primary cells, etc.), although several existing issues and knowledge gaps needs to be worked out in gaining translational confidence. This presentation will focus

on the utility of relative activity (RAF) and relative expression factor (REF) approaches in translating the in vitro kinetic data to predict pharmacokinetics and drug interactions involving hepatic and renal transporters.

SESSION II

Vitamin D Enhances Folate Transport across the Blood-Brain Barrier: Relevance to the Treatment of Cerebral Folate Deficiency

Reina Bendayan, University of Toronto

Folates are essential for brain development and function. Folate transport in mammalian tissues is mediated by three major systems, i.e., reduced folate carrier (RFC), proton-coupled folate transporter (PCFT) and folate receptor alpha (FRα). Brain folate uptake primarily occurs at the choroid plexus through the concerted actions of FRα and PCFT. Inactivating mutations on FRα or PCFT can cause cerebral folate deficiency, resulting in childhood neurodegeneration. Thus, identifying alternative routes for brain folate delivery could lead to therapeutic benefits. This presentation will address the role of RFC in folate uptake at the blood-brain barrier (BBB) and its potential regulation by ligand-activated nuclear receptors such as the vitamin D receptor (VDR), as well as highlight the potential therapeutic role of Vitamin D in the treatment of cerebral folate deficiency.

A Translational Strategy Using In Vitro Transporter Studies and In Vivo NeuroPK to Predict Human Brain Penetration of P-gp and BCRP Substances

Bo Feng, Vertex

It is of great challenge to predict human brain penetration for substrates of multidrug resistance protein 1 (MDR1) and/or breast cancer resistance protein (BCRP), two major efflux transporters at blood-brain barrier. Thus, a PBPK model with the incorporation of in vitro MDR1 and BCRP transporter function data and transporter protein expression levels has been developed. As such, it is crucial to generate MDR1 and BCRP substrate data with a high fidelity. In this study, two widely use MDR1 cell lines from Borst and NIH labs were evaluated using rodent brain penetration data. Human BCRP-MDCK cell line was also evaluated to identify BCRP substrates without the confounding of endogenous canine Mdr1. Additionally, preclinical neuroPK were used to assess in vitro-in vivo extrapolation of brain penetration in preclinical species and the ability to predict human brain penetration. Take together, a holistic approach including both in vitro transporter and in vivo neuroPK data enables a better prediction of human brain penetration of P-gp/BCRP substrates.

IVIVE of Efflux Transport using Quantitative Proteomics Approach: Importance in Prediction of Enterohepatic Recirculation

Bhagwat Prasad, University of Washington

Efflux transporters play important roles in excreting glucuronide conjugates from human liver and intestine. These conjugates can be excreted into blood for a facile renal elimination or biliary excreted into gut. The conjugated metabolites in gut can be hydrolyzed by microbiota to reactivate the parent compound allowing for enterohepatic recirculation. Our laboratory characterized the drug metabolizing enzymes, efflux transporters and bacterial glucuronidases responsible for formation, efflux and deconjugation of androgen glucuronides. Using quantitative proteomics-informed physiologically-based pharmacokinetic (PBPK) approach, we predict the quantitative significance of these individual pathways in androgen disposition. UGT2B17, an important androgen- and drug-metabolizing enzyme, is the major isoform metabolizing active androgens. This enzyme demonstrates dramatic inter-individual variability in humans, which is associated with variable efficacy and pharmacokinetics of several medications. MRP2 and MRP3 are the major transporters responsible for efflux transport of these glucuronides. Glucuronidases isolated from Bacteroides species are the major deconjugation enzymes responsible for hydrolysis of testosterone glucuronide. A systems biology-based in vitro to in vivo extrapolation approach applicable to predict impact of efflux transporters and microbiome on drug disposition will be discussed. Such in vitro cum in silico approach can be used to predict disposition of drug undergoing glucuronidation.

VENDOR PRESENTATION

An Integrated In Vitro Screen Using Sandwich-Culture Human Hepatocytes to Predict Cholestatic Hepatotoxicity

Jonathan P. Jackson, BioIVT

Cholestatic DILI in humans has been associated with bile salt export pump (BSEP) inhibition; however, in vitro BSEP IC50 concentrations do not correlate with in vivo cholestatic DILI severity. Sandwich-cultured human hepatocytes (SCHH) when treated with BSEP inhibitors respond to the resulting increased intracellular concentration (ICC) of bile acids (BA), by activation of FXR (adaptive response). This results in decreased synthesis of BA and increased expression of basolateral and canalicular efflux transporters for BA via OST alpha/beta, and BSEP which prevents cholestatic hepatotoxicity. We evaluated the time course of this adaptive response, changes in the ICC of BA, the effects of FXR antagonists, the in vivo relevance, and whether integration of FXR regulatory effects would improve the prediction of cholestatic DILI. Cryopreserved, TRANSPORTER CERTIFIED™ human hepatocytes in a sandwich configuration were cultured using QUALGRO™ Media for 5 days. On Day 5 of culture, the time course of the adaptive response was determined by evaluating the effect of cyclosporine A on the biliary excretion, and ICC of endogenous bile acids (LCMS analysis), in parallel with FXR activation (gene expression - TaqMan® primer/probe sets). Mechanistic modeling was used to determine the functional effects of mRNA based changes in FXR activation. The effect on the ER stress biomarker, CHOP, following 12 hours of exposure to CsA (10 μM), Trog (100 μM), or DY268 (5 μM) under sensitization conditions (250 μM BA pool + 1 mM free fatty acids (FFA)) was also evaluated. In a separate study, 49 compounds with varying degrees of BSEP inhibition and DILI (NIH LiverTox database) were evaluated (24 hr exposure, sensitization conditions) for their potential to affect the adaptive response. Cyclosporine A decreased the biliary excretion of endogenous bile acids in a time dependent manner, with a parallel increase in the ICC of BA, followed by activation of FXR. FXR activation resulted in a 2X increase in the biliary efflux clearance, and a 6X increase in the basolateral efflux clearance (adaptive response). Co-administration of FXR antagonists reduced the FXR mediated response to 50 and 5% of control for troglitazone and DY268, respectively. Following 12 hours of exposure, CHOP mRNA content was induced ≤ 2.0-fold above solvent control in SCHH treated with CsA (10 μM) or DY268 (5 μM) in the presence of a BA pool + FFA. CHOP mRNA content was increased to 7.1-fold above solvent control in SCHH treated with Trog (100 μM) in the presence of BA pool + FFA. Integration of the effect on the adaptive response in addition to the effect on BSEP inhibition improved the accuracy for prediction of cholestatic DILI from 22% (BSEP inhibition alone) to 95%. In addition to BSEP inhibition, integration of inhibition of basolateral efflux and/or interference with the adaptive response (FXR antagonism) allows for more accurate prediction of cholestatic DILI.

SESSION III

ITC3 Recommendations on Bile Salt Export Pump (BSEP) Inhibition Investigations and an Industry Perspective

Kunal Taskar, GSK, UK

Bile Salt Export Pump (BSEP) is an ATP-dependant membrane transport protein present in the canalicular domain of hepatocytes and contributes as an important step for bile acid secretion from hepatocytes. BSEP is essential for normal bile flow and healthy liver function. The mechanisms which cause DILI are complex and include multiple mechanisms. Therefore it is important to consider the complexity when using the in vitro BSEP inhibition data to design and select safe drugs. This ITC 3 paper gives recommendations on the proactive evaluation and understanding of BSEP inhibition in drug discovery and development.

Utility of Clinically Relevant Probe Drugs and Endogenous Biomarkers for Transporter DDI Evaluation: Perspectives from the International Transporter Consortium (ITC)

Xiaoyan Chu, Merck

Drug transporters play a critical role in the absorption and elimination of a wide range of drugs and xenobiotics. Inhibition of these transporters may cause clinically significant drug-drug interactions (DDIs). To evaluate a new molecular entity as a potential perpetrator of transporters, use of well characterized and/or clinically relevant probe substrates with good selectivity and sensitivity are critical for robust clinical DDI assessment that could inform DDI management strategy in the product labeling. Many endogenous compounds are substrates of drug transporters. Determining the impact of perpetrator drugs on the plasma or urinary exposure of these potential endogenous biomarkers in humans is being explored as an alternative approach to assess the DDI liability of drug candidates, especially in early drug development. This presentation will provide an overview of clinical probe drugs and biomarkers of key drug transporters as recommended in the recent ITC whitepaper, discuss their utility, limitations, and future direction of integrating probe drug cocktails, transporter endogenous biomarkers and mechanistic modeling to evaluate transporter-mediated DDIs.

Drug-Transporter Interactions and the Role of Transporters in Tissue and Cell Exposure – Views from Recent International Transporter Consortium White Papers

Par Matsson, Uppsala University, Sweden

In this presentation I will discuss whitepapers that emanated from the International Transporter Consortium's 3rd World Meeting in Washington DC. The focus will be on the two publications resulting from the session on Computational Modeling of Transporters, covering the use of imaging, in vitro experiments and PBPK modeling to assess the impact of transporters on cellular and tissue drug distribution, and the use of molecular modeling to identify and rationalize drug-transporter interactions. Current state-of-the-art in measuring and modeling transporter-mediated tissue and cellular drug distribution, and in molecular modeling of membrane transporters will be discussed, focusing on applications in drug discovery and development.

The Latest in Clinical Transporter DDI Evaluation: ITC3 Updates

Maciej J. Zamek-Gliszczynski, GlaxoSmithKline

This presentation will highlight the state-of-the-art in transporter clinical probes based on ITC3 whitepapers (*Clin Pharmacol Ther* 104, November 2018). Special emphasis will be placed on emerging transporters of clinical relevance and transporters with recent advances in their clinical evaluation approaches. For example, OCT1 was shown recently to be the rate-determining step in the clearance of several drugs in humans (e.g., sumatriptan, ondansetron, tropisetron, fenoterol, etc.), and thereby a mechanism of pharmacogenetic variability and DDIs. OCT1 modulation impacts metformin response, but not pharmacokinetics, and therefore OCT1 inhibition is a driver for the conduct of a metformin DDI study, but metformin is not a preferred clinical OCT1 probe drug. Similarly, P-gp inhibition can trigger a digoxin safety study, but digoxin is neither a specific nor sensitive P-gp probe. Dabigatran etexilate has been proposed as a specific intestinal P-gp probe, and is particularly sensitive when administered as a microdose. Clinical investigation of BCRP DDIs has been controversial in part due to a lack of consensus on clinical probes and inhibitors, which has now been reached. Oral sulfasalazine (immediate release) is the best available clinical probe for intestinal BCRP, oral rosuvastatin for both intestinal and hepatic BCRP, and intravenous rosuvastatin for hepatic BCRP. Ultimately, selection of clinical probes depends on co-medication relevance and the specific questions being addressed (e.g. direct characterization of a DDI with a likely co-medication or description of a DDI via a specific mechanism for extrapolation to other drugs). For example, pitavastatin is not commonly used but is the most selective clinical OATP1B1 probe. In contrast, atorvastatin and rosuvastatin are the most commonly used statins but are less selective for OATP1B1/3 and these DDIs must at a minimum consider CYP3A4 and BCRP/OATP2B1 modulation, respectively. Finally, emerging transporter biomarkers, and their future potential use in drug development will be discussed.

VENDOR PRESENTATION

Accepting the Challenges of Regulatory Guidnace

Zsuzsanna Gáborik, Solvo Biotechnology

In this talk, I will summarize efforts taken by SOLVO to address the increasing expectations of regulatory agencies, increase our knowledge of transporter assays, and improve DDI prediction based on these assays. A thorough characterization of potentiation of transporter inhibition by preincubation (also known as time-dependent inhibition) of SLC transporters beyond the OATPs can help us to understand the relevance and potential mechanism of this phenomenon. In addition, calibration of predictive values of in vitro assays allow further refinement of cut-off criteria in addition to giving further insight into the importance of the probe substrate and assay type. Finally, characterization of endogenous biomarker transport in vitro, in addition to a comparison of human and preclinical species gives a greater capacity to address key scientific questions.

PLENARY LECTURE

The Ins and Outs of An Overlooked Bile Acid Transporter, OSTα/β

Kim L. R. Brouwer, UNC Eshelman School of Pharmacy

The organic solute transporter alpha/beta (OSTα/β), designated as SLC51A/B, is one of the newest members of the solute carrier family. OSTα/β plays a key role in bile acid homeostasis. Recently, we discovered that OSTα/β protein expression is increased in liver tissue from patients with nonalcoholic steatohepatitis. The structure, function, and localization of OSTα/β will be reviewed in this presentation. Drug interactions with OSTα/β identified using our novel OSTα/β-overexpressing cell-based system will be discussed. Recent findings suggest that OSTα/β may have important clinical implications for bile acid and drug disposition and drug-bile acid interactions in health and disease.

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BIOGRAPHIES

DALLAS BEDNARCZYK, PH.D., Novartis: Dr. Dallas Bednarczyk is an Investigator in the Department of Metabolism and Pharmacokinetics at Novartis. He earned his doctorate under the supervision of Steve Wright at the University of Arizona. Dallas began his career in the pharmaceutical industry developing and implementing transporter assays as a Post-Doctoral Scientist at Sanofi-Synthelabo in 2002. Since then he has investigated aspects of transporter-mediated absorption, distribution, and excretion of drugs, as well as drug-drug interactions involving transporters. His current role at Novartis involves developing strategy around transporter issues and identifying and implementing suitable solutions to address project teams' needs regarding the transporter-mediated flux of molecules including, potential drug interactions, BBB penetration, liver targeting, and addressing in vitro/in vivo clearance disconnects due to transport.

REINA BENDAYAN, PH.D., University of Toronto: Dr. Reina Bendayan is a Professor, Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto and Career Scientist, Ontario HIV treatment Network, Ministry of Health of Ontario. After obtaining a Bachelors of Sciences in Pharmacy and a Hospital Pharmacy Residency Program at the University of Montreal, Dr. Bendayan completed a Doctor of Pharmacy at the University of Florida and a three year Medical Research Council Post-Doctoral Fellowship Program in Clinical Pharmacology and Membrane Cell Biology at the University of Toronto. Dr. Bendayan's research program is primarily focused on Membrane Transport and Therapeutics with an emphasis in the field of HIV/AIDS Antiviral Drug Transport and Regulation at sanctuary sites and cellular reservoirs of HIV. Her research program is primarily funded by CIHR and NSERC. She is the author of over 100 peer-reviewed manuscripts and has supervised many graduate students and post-doctoral research fellows. She is a member of several scientific associations: AAPS, ASPET, IBBS, IAS and CSPS. Dr. Bendayan was elected FELLOW of the AAPS and CSPS, and received the Association of Faculties of Pharmacy of Canada Research Career Award. She is also the recipient of a five-year Career Scientist Award from the Ontario HIV Treatment Network. Dr. Bendayan served as Graduate Coordinator (1998-2003), Chair and Associate Dean Graduate Education of the Graduate Department of Pharmaceutical Sciences (July 2005-July 2011) and as Acting Dean of the Leslie Dan Faculty of Pharmacy (2007).

LESLIE Z. BENET, PH.D., UCSF School of Pharmacy: Dr. Leslie Benet, Professor and former Chair (1978-1998) of Bioengineering and Therapeutic Sciences, UCSF, received his AB, BS and MS from the University of Michigan, PhD from UCSF and nine honorary doctorates. Dr. Benet served as President of the Academy of Pharmaceutical Sciences (1985) and in 1986 was a founder and first President of the American Association of Pharmaceutical Scientists (AAPS). He was elected to membership in the National Academy of Medicine of the US National Academy of Sciences in 1987. More recent honors include the 2015 ISSX North American Scientific Achievement Award; the 2016 Remington Honor Medal from the American Pharmacists Association; and in 2017 a full day symposium in his honor entitled "The Cutting Edge in Pharmaceutical Sciences—50 Years of Progress Celebrating Les Benet's 80th Birthday" in conjunction with the Pharmaceutical Sciences World Congress in Stockholm, Sweden. Dr. Benet has published over 580 scientific articles and book chapters, holds 12 patents and served as editor of 7 books. His H-factor on Clarivate Analytics is 80 with his peer-reviewed publications cited more than 27,000 times; while on Google Scholar the values are H-factor 96 and more than 42,000 citations.

KIM L.R. BROUWER, PHARM.D., PH.D., UNC Eshelman School of Pharmacy: Dr. Brouwer is Associate Dean for Research and Graduate Education, UNC Eshelman School of Pharmacy, and Kenan Distinguished Professor in the School of Pharmacy and Curriculum in Toxicology at the University of North Carolina at Chapel Hill. Her research program (supported by NIH since

1991) is focused on hepatobiliary drug disposition, hepatic transport proteins, and development/refinement of in vitro models to predict in vivo hepatic drug disposition, drug interactions, and hepatotoxicity. Dr. Brouwer was founding Director of the UNC Pharmacokinetics/Pharmacodynamics Fellowship Program, and is Co-PI of an NIH-funded Postdoctoral T32 Training Program in Clinical Pharmacology. She has mentored a diverse group of trainees (42 clinical pharmacology fellows, 28 postdoctoral fellows/visiting scholars, 34 PhD students, and numerous undergraduate/honors students), and published >225 research papers, reviews and book chapters. Dr. Brouwer is co-inventor of B-CLEAR® and co-founder of Qualyst Transporter Solutions, a UNC spin-off company recently acquired by BioIVT. She is a member of the International Transporter Consortium Steering Committee, a member of editorial advisory boards (*Clinical Pharmacology and Therapeutics*, *CPT Pharmacometrics & Systems Pharmacology*, *Clinical and Translational Science*, *AAPS Journal*), and has served as a member of the ASCPT Board of Directors (2014-2017), NIH Pharmacology Study Section (1998-2002), NIH Quantitative and Systems Pharmacology Working Group (2010-2012), and co-Chair of the NICHD Pediatric Transporters Working Group (2012-2015). Dr. Brouwer was recognized as an AAPS Fellow in 1998, and received the 2001 PhRMA Foundation Award in Excellence in Pharmaceutics, and the 2018 ASCPT-FDA Abrams Award. In 2009, Dr. Brouwer was named a Kenan Distinguished Professor, one of the highest honors bestowed on UNC faculty.

XIAOYAN CHU, PH.D., Merck: Dr. Xiaoyan Chu is a Senior Principle Scientist in the Department of Pharmacokinetics, Pharmacodynamics & Drug Metabolism (PPDM), Merck & Co., Inc., Rahway, NJ. She received her Ph.D. from the Department of Molecular Pharmacokinetics, Graduate School of Pharmaceutical Sciences, University of Tokyo, Japan. After completing her post-doctoral research at the Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, she joined the Department of PPDM at Merck & Co. Currently, her main responsibilities are to develop and lead transporter strategies to support Merck discovery and development programs, and to evaluate and establish new technologies to study the role of drug transporters in drug disposition and drug-drug interactions. She has over 60 original publications in the area of membrane transporters and pharmacokinetics. She is a member of the International Transport Consortium (ITC) and an invited speaker, organizer and steering committee member of various scientific meetings/organizations.

AYMAN EL-KATTAN, B. PHARM., PH.D., Pfizer: Dr. Ayman El-Kattan is a Senior Director and DMPK head of IFM Therapeutics. Before, he was Associate Research Fellow at the Pharmacokinetics, Dynamics, and Metabolism Department, Pfizer Inc. He earned his bachelor degree in pharmacy with distinction from University of Jordan and a Ph.D. in Basic Pharmaceutical Sciences at University of South Carolina in the US. His main research interests are focused on understanding the role of transporters in influencing drug disposition and oral absorption. Also, it involves studying the utility of physiological based pharmacokinetic modeling (PBPK) tools in projecting drug disposition and drug-drug interaction liabilities in man for new molecular entities (NME). He is also an Adjunct Professor at College of Pharmacy-University of Rhode Island in Rhode Island, US where he lectures in the graduate-level pharmacokinetic courses and serves as external advisor on dissertation committees. Dr. El-Kattan is a reviewer for several journals and an active member of the American Association of Pharmaceutical Scientists (AAPS). He has been invited speaker over 50 times at national and international conferences and meetings and has published over 100 papers in peer-reviewed Journals, book chapters and proceedings. Dr. El-Kattan also published a book titled Oral Bioavailability Assessment, Basics and Strategies for Drug Discovery and Development by Wiley.

BO FENG, PH.D., Vertex: Dr. Feng is currently a Scientific Fellow 1 in Drug Metabolism & Pharmacokinetics group at Vertex Pharmaceuticals. She earned her Ph.D. from the Department of Pharmaceutical Sciences of University of Nebraska Medical Center in 1999. Following graduate school, she completed a postdoctoral fellowship with Professor Kathleen Giacomini in the Department of Biopharmaceutical Science at University of California, San Francisco. In 2002, Bo joined Pfizer to lead a drug transporter group. Recently she joined Vertex Pharmaceuticals, and continues to work on drug transporter related ADME for

drug discovery and development projects. Her research interests include using transporter studies to predict in vivo transporter-mediated drug-drug interaction, toxicity, drug disposition and clearance. She has authored and coauthored more than 50 research papers and has given invited oral presentations at many scientific conferences.

MARIA FITZGERALD, Sanofi: Maria Fitzgerald is a Scientific Director and Head of Early ADME, DMPK, Sanofi US based in Waltham, MA. She has been at Genzyme and then Sanofi for more than 17 years and is currently responsible for physicochemical profiling, in vitro drug metabolism and transporter studies for drug discovery and development. Earlier in her career at Genzyme, she was responsible for pharmaceutics and analytical characterization of drug candidates. Prior to Genzyme, Maria was a group leader for the chromatography, environmental and inorganic analysis group in the R&D organization at Polaroid Corporation. Maria earned her Bachelor of Science in Chemistry from LeMoyne College, Syracuse, NY and her Master of Science from Boston College where she studied bio-inorganic chemistry.

ZSUZSANNA GÁBORIK, PH.D., Solvo Biotechnology: Dr. Gáborik received her MSc Degree in Bioengineering from University of Technology and Economics, Budapest. She earned her Ph.D. in Cellular and Molecular Physiology at the Semmelweis University, Budapest, and started her academic carrier at Department of Physiology at the Semmelweis University. She joined SOLVO in 2011 and started working in the Business Development team, with responsibility for service and product launches, scientific sales support, and participated as an editor on SOLVO's Transporter Book. In 2015 she joined the Research and Development Department as a Scientific Development Manager responsible for assay development, and in 2016 took over the operational management of SOLVO's research and development activities as Head of the R&D Laboratory. She is the author of 17 peer reviewed scientific publications.

JONATHAN P. JACKSON, PH.D., BioIVT: Dr. Jonathan P. Jackson, DABT, has over 12 years of experience in ADME-Tox working across a diverse chemical space including pharmaceutical, consumer products, food additive, and industrial chemicals. His professional experience has primarily focused on human in vitro models with specific emphasis on metabolism, transport, and gene regulation mechanisms which together play a significant role in drug/xenobiotic exposure, affecting absorption, elimination, and toxicity.

STEVEN W. LOUIE, BioIVT: Steven is the Director of Transporter Sciences for BioIVT in Durham, NC. He lives in the Greater Boston Area, and mostly telecommutes to his home base. He was formerly a Senior Scientist in the Department of Pharmacokinetics and Drug Metabolism in Amgen, Cambridge, MA. He did his undergraduate work at the University of Minnesota (Minneapolis/St. Paul, MN) and his graduate work at the University of Iowa (Iowa City, IA). He is a transporter jockey who has been developing and implementing in vitro tools and assays to support drug discovery and development for the last 22 years. He is the 2017-2018 Chair of the AAPS Drug Transport Focus Group (DTFG). He is the 2017 AAPS Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM) Sections Service Award Recipient, and has the honor of co-organizing the AAPS Workshop "Transporter Boot Camp: Back to Basics," the eLearning Course "Transporter Knowledge for New Frontiers" and the 2018 AAPS Transporter Workshop-From Benchside to Bedside. This year he has the honor of contributing to The Boston Society HT-ADME Conference. Prior to joining BioIVT, Steven worked at Amgen, Merck and GSK. His recent research interests include in vitro/in vivo extrapolation to predict transporter-mediated drug-drug interactions. His recent work has contributed to the recent IND-filing, FDA and/or EMA approvals of Corlanor™, Kryprolis™, Parsabiv™.

JOSÉ E. MANAUTOU, PH.D., University of Connecticut: José E. Manautou is the Interim Department Head of Pharmaceutical Sciences, Assistant Dean of Graduate Education and Research and Professor of Toxicology at the University of Connecticut School of Pharmacy. His long-term research interests are on biochemical and molecular mechanisms of xenobiotic-induced

hepatotoxicity and defining compensatory responses to liver injury that enhance tissue resistance to toxicant re-exposure (i.e., adaptation). In his twenty years as an educator, Dr. Manautou has contributed to the training of 2,000 pharmacy students. His teaching expertise is in pharmacology and toxicology. In addition, he has taught to nearly 4,000 non-pharmacy students a basic toxicology course entitled, "*Toxic Chemicals and Health*". He has trained multiple Ph.D., MS graduates and postdoctoral fellows. Dr. Manautou has published over 200 originally research articles, abstracts, commentaries and other reports. He has been the principal and co-investigator of numerous extra- and intramural grants. His service to the scientific community and to the discipline of toxicology is exemplary. In 2003, Manautou was elected councilor of the Society of Toxicology (SOT) and has served in key committees and task forces of the society. He was the recipient of the 2006 Achievement Award of the SOT. Dr. Manautou has served as member of review panels for the National Academies of Sciences, Medicine and Engineering. His involvement in the review of extramural and intramural science for the National Institutes of Health (NIH) has been also significant. He was member of the NIH Xenobiotic and Nutrient Disposition and Action Study Section, NIH College of CSR Reviewers, and the NIEHS Board of Scientific Counselors. Currently, he is a member of the National Advisory Environmental Health Sciences Council and the Food and the Drug Administration's Nonprescription Drugs Advisory Committee. He is also on The Board of Trustees for the Health and Environmental Sciences Institute (HESI). Dr. Manautou is Associate Editor of *Toxicology and Applied Toxicology*, and is also a member of the editorial board of seven other journals. He is also the new Co-Editor-in-Chief of the journal *Current Opinions in Toxicology*. He obtained his BS in pharmacy from the University of Puerto Rico, Ph.D. in pharmacology and toxicology at Purdue University in 1991, and postdoctoral training at the University of Connecticut. He also conducted sabbatical training at the Academic Medical Center in Amsterdam.

PÄR MATSSON, PH.D., Uppsala University, Sweden: Dr Matsson is Associate Professor in Pharmaceutics at Uppsala University, Sweden. He is also Program Director for the Master's Program in Pharmaceutical Modeling at the Uppsala University Faculty of Pharmacy. His research is centered on the development of new experimental and computational methods to quantitate and visualize drug distribution at the tissue, cellular and subcellular scales, and on applying these methods to understand how the chemical features of drug molecules determine their cellular transport and targeting to specific subcellular compartments. His research interests also include how ligands outside the traditional small-molecule chemical space—in particular unusually large bioactive molecules—can be successfully developed into drugs. He is the recipient of the AAPS Excellence in Graduate Research Award, the AAPS Meritorious Manuscript Award, and the APhA Ebert Prize. Dr Matsson received his MSc and PhD in Pharmaceutical Sciences from Uppsala University, and held a Post Doctoral Fellowship at the University of California San Francisco. He joined the International Transporter Consortium in 2014, and its Steering Committee in 2017.

BHAGWAT PRASAD, PH.D., University of Washington: Dr. Bhagwat Prasad is an assistant professor in the Department of Pharmaceutics, University of Washington (UW), Seattle, WA. He leads several federally- and industry-funded research programs on characterization of interindividual variability in drug disposition (drug transport and metabolism). He serves as a director of the UW proteomics-based research in non-cytochrome P450 enzymes (PRINCE) and he is affiliated with the UW research affiliate program on transporters (UWRAPT) as co-director. Dr. Prasad has published >70 peer-reviewed articles and >80 conference abstracts and delivered 50 invited talks at various conferences such as ASPET (EB), ISSX, and ACCP. Dr. Prasad is the recipient of 2018 ISSX North American New Investigator Award and his work was also selected for the Early Career Faculty Showcase at the 2018 ASPET meeting. Dr. Prasad also serves as a Secretary-elect of the Drug Metabolism and Disposition Division of ASPET. He co-organized 2018 ISSX workshop on quantitative proteomics and is a member of organizing committee for the 12th international ISSX meeting, 2019 to be held in Portland. Dr. Prasad is a member of editorial board of Drug Metabolism and Disposition. Dr. Prasad obtained his MS in 2006 and Ph.D. in 2010 in Pharmaceutical Sciences from NIPER, Mohali, India.

HONG SHEN, PH.D., Bristol-Myers Squibb: Dr. Hong Shen currently is a Principal Scientist in the Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Company, where he researches drug transporter activities and provides preclinical DMPK support for multiple drug discovery and development programs. He earned his doctorate under the supervision of David Smith of the University of Michigan, where his research focused on the role of PEPT2 transporter in drug renal tubular reabsorption and brain penetration. His areas of expertise in DMPK include drug transporters, drug-drug interactions, and PK/PD modeling. His research is focused towards mechanistic-based approaches to explain the handling of drugs, metabolites and endogenous biomarkers within eliminating organs, namely the liver and kidney, via the examination of relevant processes of transport and metabolism. Dr. Shen has published over 60 original articles and chapters. He was the recipient of the James R. Gillette Drug Metabolism and Pharmacokinetics Awards selected by the Drug Metabolism Division of ASPET in 2001, 2007 and 2018. He currently is a committee member of the International Transporter Consortium (ITC); AAPS Drug Transport Focusing Committee, and Pharmaceutical IQ DMLG/CPLG Transporter Working Group.

KUNAL TASKAR, PH.D., GlaxoSmithKline: Dr. Taskar is currently working as Scientific Leader & Associate GSK Fellow at GlaxoSmithKline, U.K. in DMPK, IVIVT R&D department. His past experience includes working as a drug transporter expert in the DMPK Pharmaceutical Candidate Optimization department at Biocon Bristol-Myers Squibb Research and Development. Kunal completed his doctorate in Pharmaceutical and Biomedical Sciences and postdoctoral research at Texas Tech University Health Sciences department in Quentin Smith's lab with research focused on drug delivery to central nervous system and role of transporters in drug delivery across the blood-brain barrier (BBB). Kunal's experience and research focus include: Modelling and Simulation to support DDI predictions, dose predictions, special populations and disease state exposures, drug-drug interaction predictions and mechanistic understanding of the clinically occurring drug–drug interactions and toxicity; transporter mediated drug delivery and intracellular drug concentrations, especially the role of uptake transporters in drug pharmacokinetics-pharmacodynamics; novel transporters and role in drug disposition; improvising current transporter assays and models for drug transporter studies and clinical predictions; and drug-transporter mediated interactions for endogenous transporter substrates.

MANTHENA V. VARMA, M.S., PH.D., Pfizer: Dr. Manthena Varma, PhD is Associate Research Fellow, at Pfizer Inc. Dr. Varma received his B. Pharm. degree from the Kakatiya University, India in 2000, and an M.S. degree (2001) and PhD in Pharmaceutics (2005), from the National Institute of Pharmaceutical Education and research (NIPER), Punjab, India. Later, Dr. Varma worked as a Post Doctoral Fellow at the Department of Pharmaceutics, University of Minnesota (Minneapolis). In 2008, he joined Worldwide R&D, Pfizer, Groton, CT. Dr. Varma holds an Adjunct faculty position in the Department of Pharmacy of the University of Rhode Island. Manthena is a founding member and Instructor for a three-day Annual workshop on "Transporters in Drug Discovery and Development: Driving Knowledge from Laboratory to Label" at University of Rhode Island. He is member and ex-chair (2017-18) of North Jersey Drug Metabolism Discussion Group. His research is focused in the fields of ADME/PK technologies and strategies in drug design and development, role of drug transporters and transporter-enzyme interplay (extended clearance) in ADME/PK, clinical pharmacokinetics and DDI predictions/evaluation via mechanistic (PBPK) modeling. He published about 100 original articles/reviews/book chapters and presented over 60 presentations at the scientific conferences in these scientific areas.

GUANGQING XIAO, PH.D., Sunovion: Dr. Guangqing Xiao is a Director of DMPK at Sunovion. Dr. Xiao received his B.S and M.S. from Peking University, and Ph.D. from Boston University. After completing his postdoctoral research at University of California at San Francisco, he worked at BD Bioscience, Biogen and Takeda, where he led the transporter groups in developing new assays and evaluating the role of transporters in drug disposition and DDIs. Dr. Xiao recently joined the Clinical Pharmacology Department at Sunovion. Dr. Xiao has 25 papers in Biopharmaceutics and Biochemistry related area.

MACIEJ J. ZAMEK-GLISZCZYNSKI, PH.D., GlaxoSmithKline: Maciej Zamek-Gliszczynski has 15 years of industry (Eli Lilly and GSK) experience in supporting DMPK and PK/PD aspects of oncology, endocrine/metabolic, and infectious disease programs at all stages between discovery, clinical development, and post-marketing. He is currently leading Quantitative Drug Disposition, a world-wide group responsible for mechanistic understanding of PK and DDIs in the GSK portfolio. Dr. Zamek-Gliszczynski's research is focused on clinical PK/PD and DDI implications of drug and metabolite transport. He is the author of >100 manuscripts and presentations on this subject (>4,000 cites, h¬-index = 31). He serves on the editorial boards of *Pharmaceutical Research* and *Drug Metabolism and Disposition*. Dr. Zamek-Gliszczynski is a member of the International Transport Consortium (ITC) steering committee, was past chair of AAPS PPDM section and AAPS Drug Transport FG, as well as GSK management representative on IQ DMLG. He has been active in organizing DMPK/clinical pharmacology meetings, including several AAPS and ITC/ASCPT Workshops. Dr. Zamek-Gliszczynski lectures in graduate-level PK/PD courses and serves as external committee advisor (including as adjunct prof at UNC). He enjoys developing scientists and has an established mentorship record at the associate scientist, junior and peer Ph.D., as well as graduate student and post-doc levels.

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CYPROTEX (www.cyprotex.com) was founded in 1999 and specialises in in vitro and in silico ADME-Tox. The company has sites in the UK and the US. In 2016, Cyprotex was acquired by Evotec AG (www.evotec.com). As a whole, the Group offer integrated and stand-alone drug discovery capabilities as well as full CMC and IND-enabling services, allowing the company to provide expert support across the value chain from early discovery through to preclinical development and beyond.

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Sincerely,

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