HT-ADME

A BOSTON SOCIETY CONFERENCE

2021

WEBINAR

TUESDAY & WEDNESDAY,
JUNE 22-23, 2021

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ORGANIZERS' WELCOME

Welcome to the 2021 HT-ADME Conference.

Our organizers have gathered another excellent group of speakers for the annual HT-ADME conference. 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

PRESIDING OFFICERS

Conference Chair:
Maria Fitzgerald, Sanofi
Conference Chair Elect:
Ruchia Duggal, Merck

COMMITTEE MEMBERS

Steven Louie, Novartis
Dallas Bednarczyk, Novartis
Nimita Dave, Black Diamond Therapeutics
John S. Janiszewski, NIH/NCATS
Mitesh Patel, Novartis
Chris Rowbottom, Moderna
Wilson Shou, BMS
Ron Xu, ORIC Pharmaceuticals
Hui Zhang, Pfizer

HT-ADME 2021 CONFERENCE AGENDA

DAY 1: TUESDAY, JUNE 22

10:00 - 10:05 AM **Conference Opening & Plenary Speaker Introduction**
Maria Fitzgerald, Sanofi

10:05 - 10:45 AM **PLENARY: Liquid Biopsy in ADME: Where are We Now and Where are We Going?**
David Rodrigues, Pfizer

10:45 - 10:55 AM **Q & A**

SESSION I: Impact of Free Fraction in ADME

10:55 - 11:00 AM **Session Introduction**
Chris Rowbottom, Moderna & Ruchia Duggal, Merck

11:00 - 11:30 AM **Improved IVIVE for Hepatic Clearance Prediction: The Impact of Albumin on Hepatic Uptake**
Na Li, C4 Therapeutics

11:30 - 11:40 AM **Q & A**

11:40 - 12:25 AM **Unbound Volume of Distribution as a Foundational Parameter in Drug Design**
Randy Miller, Merck & Iain Martin, Relay Therapeutics

12:25 - 12:35 PM **Q & A**

12:35 - 1:25 PM **LUNCH BREAK & SPONSOR SHOWCASE**

1:25 - 1:30 PM **Introduction**
Chris Rowbottom, Moderna

1:30 - 1:55 PM **High Throughput Physical Chemistry Assays: Advances and Application**
Mark Wenlock, Cyprotex

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1:55 - 2:00 PM **Q & A**

SESSION II: In Silico ADME

2:00 - 2:05 PM **Session Introduction**
John Janiszewski, NIH

2:05 - 2:35 PM **NCATS ADME Datasets and In Silico Models Derived from these Datasets**
Xin Xu, NIH

2:35 - 2:45 PM **Q & A**

2:45 - 2:50 PM **Introduction**
Wilson Shou, BMS

2:50 - 3:15 PM **Mechanistic Insights Into the Inhibitor Preincubation Effect**
Peter Tatrai, SOLVO

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3:15 - 3:20 PM **Q & A**

3:20 - 3:40 PM **HT-DMPK: From Data to Knowledge. Generate Data to Feed AI Model Generation and Reach Optimal Compound Design**
Ismael Zamora, Molecular Discovery

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3:40 - 3:45 PM **Q & A**

3:45 - 3:50 PM **Plenary Speaker Introduction**
John Janiszewski, NIH

3:50 - 4:30 PM **PLENARY: Influencing Design with in silico ADME Models**
Marcel Hop, Genentech

4:30 - 4:40 PM **Q & A**

DAY 2: WEDNESDAY, JUNE 23

SESSION III: ADME for New Modalities

10:00 - 10:05 AM **Session Introduction**
Steven Louie, Novartis & Dallas Bednarczyk, Novartis

10:05 - 10:35 AM **AAV Gene Therapies - new opportunities for ADME Scientists**
Mark Milton, Novartis

10:35 - 10:45 AM **Q & A**

10:45 - 11:15 AM **Quantitative and Qualitative Aspects of PROTAC Metabolism: Do they differ from small molecule?**
Beth Williamson, AstraZeneca, UK

11:15 - 11:25 AM **Q & A**

11:25 - 11:50 AM **VENDOR PRESENTATION: IVAL**
999Elite™ Cryopreserved Human Hepatocytes
Albert Li, IVAL

IVAL
In Vitro ADMET Laboratories, Inc.

11:50 - 11:55 PM **Q & A**

11:55 - 1:00 PM **LUNCH BREAK & SPONSOR SHOWCASE**

SESSION IV: Drug Accumulation/Transporters

1:00 - 1:05 PM **Session Introduction**
Mitesh Patel, Novartis & Hui Zhang, Pfizer

1:05 - 1:35 PM **The Impact of Ion Trapping on the Cellular Accumulation of Highly Permeable Low Molecular Weight Acidic Drugs**
Dallas Bednarczyk, Novartis

1:35 - 1:45 PM **Q & A**

1:45 - 2:15 PM **Validation of PXB Chimeric Mice with Humanized Liver to Predict Human Liver-to-Plasma Kpuu of OATP1B1 Substrates**
Bo Feng, Vertex

2:15 - 2:25 PM **Q & A**

2:25 - 2:55 PM **Drug Interaction Mediated by Transporter Induction: Current Status and Perspective**
Xinning Yang, FDA

2:55 - 3:05 PM **Q & A**

3:05 - 3:15 PM **VENDOR PRESENTATION: BioIVT**
Importance of Polarized Models for the Evaluation of Hepatic Transporter Based Drug Interactions
Kenneth R. Brouwer, BioIVT

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3:15 - 3:20 PM **Q & A**

SESSION V: COVID19 and ADME

3:20 - 3:25 PM **Session Introduction**
Maria Fitzgerald, Sanofi & Steven Louie, Novartis

3:25 - 4:05 PM **PLENARY: High Throughput Screening and Real World Biomarkers to Predict Drug-Drug and Drug-Nutrient Interactions: Implications to polypharmacy associated with COVID**
Kathy Giacomini, UCSF

4:05 - 4:45 PM **PLENARY: ADME data on Remdesivir/Treatment Efficacy**
Yurong Lai, Gilead

4:45 - 5:00 PM **Panel Discussion**

5:00 - 5:05 PM **CLOSING REMARKS**

ABSTRACTS

PLENARY

Liquid Biopsy in ADME: Where are we now and where are we going?

David Rodrigues, Pfizer

Various clinical tools have been developed to support the study of genotype-phenotype associations and drug-drug interactions (DDI) involving drug-metabolizing enzymes (e.g., cytochromes P450, CYP) and drug transporters. These have included probe drugs and endogenous compounds in plasma and urine that present as biomarkers. More recently, attention has turned to "liquid biopsy" methods, which involve the profiling (proteomics and CYP activity) of immunocaptured cargo-laden tissue-specific extracellular vesicles (EV) present in human blood. The presentation will briefly describe the isolation, characterization, and profiling of serum EV (mixtures of exosomes and small microvesicles) in support of CYP and organic anion transporting polypeptide (OATP) profiling. Examples include CYP2D6 genotype-phenotype associations, CYP3A5 genotype-liver protein expression profiling, differentiation of gut CYP1A2 versus CYP3A4 activity, induction profiling (liver CYP3A4, CYP2D6, OATP1B1, and OATP1B3) following an inducer, and expression profiling of serum-derived liver EV from pregnant versus non-pregnant females. With further validation and wider use, it is envisioned that the EV-based liquid biopsy approach will be deployed alongside established drug probe-based methods and emergent drug transporter biomarkers. Such advancements are warranted because of the absence of CYP biomarkers (beyond CYP3A4/5), increasingly complex DDI involving gut and/or liver CYP3A4/5, and questions regarding transporter induction.

SESSION I

Improved IVIVE for Hepatic Clearance Prediction: The Impact of Albumin on Hepatic Uptake

Na Li, C4 Therapeutics

Accurate human PK prediction is pivotal in the early stages of drug discovery to manage human dose projection, estimate efficacy and safety margins in an integrated manner. Hepatic clearance prediction remains an active area of research and suffers from significant gaps, especially when active transport is involved. The present work investigated the impact of addition of albumin at physiological relevant concentration on unbound hepatic uptake CL and Kpuu in preclinical species and human. Various in vitro to in vivo extrapolation (IVIVE) approaches were evaluated to predict hepatic CL driven by uptake transporters in rat, cynomolgus monkey and human. These results suggest supplementing 4% BSA in hepatocyte uptake assay provides a useful tool to characterize hepatic uptake CL for OATP substrates, enabling more accurate hepatic CL prediction in rat and human with no need of empirical scaling factor. In addition, cynomolgus monkey is proven to be a useful preclinical species to validate the IVIVE strategy to strengthen the confidence of human CL predication. Taken together, the study provided a practical mechanism-based IVIVE strategy to enable chemistry prioritization based on human hepatic CL prediction in early drug discovery, when active uptake transport is involved in drug disposition and elimination.

Unbound Volume of Distribution as a Foundational Parameter in Drug Design

Ian Martin, Relay Therapeutics & Randy Miller, Merck

In this talk, we will discuss unbound volume of distribution (VSS,U) as a fundamental drug property. Specifically, we will discuss the role of Vss,U as the true (but often ignored) drug depot and how it is central in determining both the potency required for target engagement as well as the elimination

rate to achieve an appropriate half-life. We will argue that targeting individual drug parameter values is not a rational approach to drug discovery; instead we propose focusing on key parameter ratios (*Miller et al., J. Med. Chem. 2020, 63, 21, 12156–12170*)

VENDOR PRESENTATION

High Throughput Physical Chemistry Assays: Advances and Application

Mark Wenlock, Cyprotex

Physical chemistry plays a pivotal role supporting rational drug design by connecting the molecular structure of a compound to its biological effects. Often, successful, small-molecule drug-design strategies are supported by physicochemical insight, principally aqueous solubility and lipophilicity. This presentation will discuss variations and advances in experimental methodology that address modern expectations and the application of such in vitro data, generated using different assay variants, within the drug discovery process.

SESSION II

Mechanistic insights into the inhibitor preincubation effect

Péter Tátrai, Solvo

Time-dependent inhibition of OATP1B1 by cyclosporin A (CsA), i.e. the potentiation of in vitro transporter inhibition upon prolonged preincubation with CsA, was described more than a decade ago. For years to follow, the phenomenon was thought to be limited to OATP1B transporters and a handful of compounds with no obvious relatedness in the chemical space. In our earlier work we have shown that potentiation of transporter inhibition by preincubation, or PTIP, affects multiple pharmacologically relevant solute carrier transporters and is thus more prevalent than previously believed, and large hydrophobic inhibitors are more likely to display PTIP. Here we further investigate the potential mechanism of PTIP with a focus on the involvement of protein binding. We also assess whether PTIP may affect efflux transporters of the ABC family such as MDR1, and if this needs to be taken into account when designing and interpreting vesicular transport and vectorial transport (monolayer) assays. Our data indicate that while the extent of PTIP in uptake inhibition assays may depend on extracellular protein concentration, significant PTIP remains even in the presence of 5% w/v BSA. This confirms the need for preincubation to establish relevant inhibitory potencies regardless of the amount of protein in the incubation media. On the other hand, and in line with the proposed mechanism, preincubation had little or no impact on inhibition in monolayer and vesicular transport assays, respectively.

HT-DMPK: from data to knowledge. Generate data to feed AI model generation and reach optimal compound design

Ismael Zamora, Molecular Discovery

High Throughput Screening in the field of Drug Metabolism and Pharmacokinetic studies during the drug discovery process can generate a huge amount of data on standardized in-vitro assays that is used among other cases: to identify potential compound liabilities that may limit the action of the compound at the site of effect, understand the interspecies differences in drug pharmacokinetic profile, discover toxicity issues related to the compound or its metabolites and to infer the adequate first dose in human.

One key factor to effectively handle the high volume generated in HTS, it is the transformation of the biological sample content into actual data, that is typically done using LC-MS (QQQ or HRMS) instrumentation. Nowadays there are a wide variety of MS instrumentation that is used to do this task, generating a huge amount of numerical data that has to be interpreted into chemical information, either numerical as properties computed like: Clearance, permeability, protein binding, etc. or structural as metabolite chemical structures. In the past years we have developed a number of tools to automate the structural elucidation of metabolites for both small and peptide molecules and more recently we have also introduce systems to compute the numerical DMPK end points from even more HTS-MS system

like MALDI based technology. Both approaches are useful to provide the needed information that can be reported back to the discovery teams to improve the DMPK properties of a compound.

Nevertheless, we would like to report in this presentation a summary of the methodology used and even move a step forward that would the use of the produced information from the MS data to learn from the structure of the compounds, the experiment definition and the information extracted to derive Machine learning models that can automatically learn from the data to monitor, update and improve the model quality in an Artificial Intelligent approach, getting the maximum knowledge from the produced data and enabling the prediction of new potential compound structures.

PLENARY

Influencing Design with In Silico ADME Models

Marcel Hop, Genentech

While the number of FDA drug approvals has increased lately and the attrition due to pharmacokinetic reasons in development is relatively small, challenges remain. The drug discovery process remains very inefficient and frequently several thousand compounds need to be synthesized in the course of a project to identify a development candidate with the right properties. Indeed, multi-parameter optimization is frequently a trial and error process. One contributing factor is that ADME scientists often do not speak the same language as medicinal chemists and, therefore, are not as influential in design of new molecules as desired. Fortunately, the large quantity of in vitro ADME data gathered over the last 10-20 years has enabled the creation of in silico models that can be used to predict various ADME properties and triage design ideas prior to synthesis of the compounds during the optimization process. In silico ADME models are available to predict in vitro ADME properties such as metabolic stability and sites of metabolism, permeability and efflux, plasma protein binding, and CYP inhibition and ultimately in vivo PK thereby reducing the time required to find compounds with the right balance of properties. Subsequently, models are available that incorporate a mix of predicted and measured properties (e.g., potency) to prioritize compounds further. The next horizon is the prediction of potency and selectivity and the latest artificial intelligence tools appear to provide promise. In this presentation, the author will discuss the value of these models and how to incorporate them effectively in lead optimization to enable rapid idea generation and ultimately optimization.

SESSION III

Quantitative and qualitative aspects of PROTAC metabolism: do they differ from small molecules?

Beth Williamson, AstraZeneca

Proteolysis Targeting Chimeras (PROTACs), are becoming an established pharmacological modality with the first examples now having reached the clinic. As more proteins are targeted, the structural and property diversity of PROTACs is now reaching a point where it is possible to begin to observe trends in their ADME properties, make comparisons to conventional "small molecules", and identify specific issues associated with their optimisation and development.

Given PROTACs breach at least one "Rule-of-5" constraint due to their high molecular weight, and face additional challenges related to their chemical structure e.g. the need to reconcile the choice of E3 ligase warhead and linker required to achieve pharmacological activity with the desired ADME properties, it is clear that their optimisation presents challenges not usually encountered with typical small molecule drugs.

In this context I will discuss some of our early observations on the pharmacokinetic properties of oral PROTACs and highlight some of the ADME challenges we have encountered, including the key experimental challenges we have faced and how this has defined our early screening cascade.

VENDOR PRESENTATION

999Elite™ Cryopreserved Human Hepatocytes

Albert P. Li, IVAL

Recent advancement in human hepatocyte isolation cryopreservation technologies in our laboratory has led to the development of 999Elite™ Cryopreserved Human Hepatocytes. The hepatocytes, upon recovery from cryopreservation, have >90% viability and form stable, >90% confluent cultures, with a culture duration of >9 days. The 999Elite™ hepatocytes exhibit robust uptake transporter activity as demonstrated by saturation kinetics and rifampin inhibition, responsiveness to CYP1A2, CYP2B6, CYP3A4, CYP2C8/8/19 induction (both mRNA and activity), and hepatotoxicity of drugs with severe in vivo hepatotoxicity (DILI drugs). Application of the 999Elite™ hepatocytes in the evaluation of efficacy and duration of efficacy of gene therapy modalities is illustrated by a recent a proof-of-principle study with HPRT1 GalNac siRNA HPRT in showing a 90% decrease in HPRT1 expression for a duration of >40 days. The 999Elite Cryopreserved Human Hepatocytes thereby represent a physiologically relevant in vitro experimental for the evaluation of human-specific drug properties. A comparison of animal and human results with 999Elite™ hepatocytes will also allow the selection of the most appropriate animal species for the assessment of human in vivo drug properties.

SESSION IV

The Impact of Ion Trapping on the Cellular Accumulation of Highly Permeable Low Molecular Weight Acidic Drugs

Dallas Bednarczyk, Novartis

Literature suggests that highly permeable low molecular weight (LMW) acidic drugs are transported by Organic Anion Transporter 2 (OAT2). However, an asymmetric distribution of ionizable drugs in subcellular organelles where pH gradients are significant may occur in the presence of an inhibitor relative to its absence (e.g. lysosomal trapping). Presented is work illustrating that OAT2-mediated transport of highly permeable LMW anions may be negligible. A rifamycin SV (RifSV) dependent reduction in the accumulation of highly permeable LMW anions previously observed in hepatocytes could be qualitatively reproduced using HepG2 cells and also in MDCK cells which lack expression of OAT2. Neither HepG2 nor MDCK cells demonstrated meaningful penciclovir transport, nor was the cellular accumulation of the highly permeable LMW anions sensitive to competitive inhibition by the neutral OAT2 substrate. Both cell lines however demonstrated sensitivity to the mitochondrial uncoupler p-trifluoromethoxy carbonyl cyanide phenyl hydrazone (FCCP) in a manner similar to RifSV. Furthermore, the transepithelial MDCK permeability of the highly permeable LMW anions was measured in the absence and presence of RifSV and FCCP. Neither RifSV or FCCP, nor the OAT2 inhibitor ketoprofen, reduced the transepithelial flux of the anions as would be anticipated for inhibition of a transported substrate. The findings presented here are aligned with cellular accumulation of highly permeable LMW anions being significantly determined by ion trapping sensitive to mitochondrial uncoupling rather than the result of OAT2-mediated transport. The outcome presented highlights a rare observation of anionic drug trapping in a compartment sensitive to mitochondrial uncoupling (e.g. the mitochondrial matrix) that may be confused for transporter-mediated uptake.

Validation of PXB Chimeric Mice to Predict Human Liver-to-Plasma Kpuu of OATP1B1 Substrates

Bo Feng, Vertex Pharmaceuticals

The ability to predict human liver-to-plasma unbound partition coefficient (Kpuu) is important to estimate unbound liver concentration for drugs that are substrates of hepatic organic anion transporting peptide (OATP) transporters with asymmetric distribution into the liver relative to plasma. Herein, we explored the utility of PXB chimeric mice with humanized liver that are highly repopulated with human hepatocytes to predict human hepatic disposition of OATPs substrates, including rosuvastatin, pravastatin, pitavastatin, valsartan and repaglinide. In vitro total uptake clearance and transporter-mediated active uptake clearance in C57 mouse hepatocytes were greater than PXB chimeric mouse hepatocytes for rosuvastatin, pravastatin, pitavastatin and

valsartan. Consistent with in vitro uptake data, enhanced hepatic uptake and resulting total systemic clearance were observed with the above four compounds in control SCID than in PXB chimeric mouse, which suggest that mouse has a stronger transporter-mediated hepatic uptake than human. In vivo liver-to-plasma Kpuu from PXB chimeric and SCID control mice were also compared, and rosuvastatin and pravastatin Kpuu in SCID mouse were more than 10-fold higher than that in PXB chimeric mouse, whereas, pitavastatin, valsartan and repaglinide Kpuu in SCID mouse were comparable with Kpuu in PXB chimeric mouse. Finally, PXB chimeric mouse liver-to-plasma Kpuu values were compared with the reported human Kpuu, and a good correlation was observed as the PXB Kpuu vales were within 3-fold of human Kpuu. Our results indicate that PXB mice could be a useful tool to delineate hepatic uptake and enable prediction of human liver-to-plasma Kpuu of hepatic uptake transporter substrates.

Drug Interaction Mediated by Transporter Induction: Current Status and Perspective

Xinning Yang, FDA

There is a growing interest in transporter induction and its clinical implication in drug pharmacokinetics and drug-drug interactions (DDIs). Induction leads to decrease in exposure of transporter substrates and thus affecting their efficacy, when those drugs are concomitantly used with transporter inducers. Compared to Cytochrome P450 (CYP) enzymes, much less is known about induction of drug transporters. There are substantial data demonstrating induction of P-glycoprotein (P-gp) by well-known CYP3A inducers probably via activation of pregnane X receptor (PXR). In contrast, there are mixed results for investigations of OATP1B induction with some studies showing that certain inducers decreased exposure of OATP1B substrates while other studies did not. The putative mechanism of OATP1B induction is not well understood. In the FDA DDI guidance, there is no recommended in vitro approach to evaluate transporter induction due to limitations of current in vitro models. This presentation will focus on P-gp and OATP1B induction, and describe 1) clinical DDI study data involving P-gp or OATP1B substrates; 2) when a clinical DDI study may be considered for investigational drugs ; 3) considerations of DDI study design especially when the DDI mechanisms involve induction and inhibition of transporters or metabolic enzymes.

SESSION V

PLENARY

High Throughput Screening and Real World Biomarkers to Predict Drug-Drug and Drug-Nutrient Interactions: Implications to polypharmacy associated with COVID treatment

Kathy Giacomini, UCSF

Individuals with serious COVID infections often have pre-existing co-morbidities and are generally older. Thus, in addition to being prescribed drugs for the treatment of COVID19 and its sequelae, many of these individuals are taking a myriad of other drugs. In this presentation, I will describe a screening study of 25 small molecule drugs in clinical trials for COVID19 against 11 drug transporters, which are targets for clinically relevant drug-drug interactions (DDIs). Our in vitro studies revealed that 20 of the 25 drugs met the criteria suggested by FDA DDI guidances to consider a clinical DDI study. Further, I will describe the analyses of real world transporter biomarkers in data from electronic health records, which suggested that several of the drugs actually do cause transporter-mediated DDIs clinially. I will end with a discussion of the propensity for many anti-microbial drugs to perpetrate clinical DDIs and drug-nutrient interactions, and the use of various biomarkers for predicting DDIs in pre- and post-marketing settings.

SPEAKER BIOGRAPHIES

DALLAS BEDNARCZYK, PHD, Novartis, Dr. Dallas Bednarczyk is an Investigator in the Department of Pharmacokinetic Sciences 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, addressing in vitro/in vivo clearance disconnects due to transport, and investigating transporter-enzyme interplay. Frequently he has the responsibility to demonstrate that transporters do not provide a solution to issues faced by project teams.

KENNETH R. BROUWER, PHD, RPH, BioIVT, Dr. Brouwer is Vice President of Technology, ADME-Tox at BioIVT, a leading provider of research models and services for drug and diagnostic development. BioIVT's ADME Tox group provides expertise and research services in the areas of hepatic drug transport, metabolism, drug interactions, transport and metabolism regulation and hepatotoxicity. Dr. Brouwer has an ongoing interest in the metabolic disease state area and in the NAFLD/NASH area in particular, with recent publications detailing the importance of the adaptive response in the liver to increased intracellular concentrations of bile acids, and the utility of in vitro biomarkers to predict in vivo effects.

Prior to this, Dr. Brouwer served as the Chief Scientific Officer at Qualyst Transporter Solutions, and as Executive Director, at PPD Discovery, where he led the scientific and administrative operations within the preclinical groups. Before joining PPD Discovery he started the Clinical PK group at GlaxoSmithKline and later served as Director, Preclinical Development. He was responsible for the DMPK issues leading to candidate selection, review of candidate project plans, and the transition from candidate selection to full development. Dr. Brouwer has led and directed large international multidisciplinary project teams and presented at FDA panel reviews.

Dr. Brouwer has over 90 publications in peer reviewed journals and is the holder of 3 patents, and co-inventor of the C-DILI™ technology (patent pending). Dr. Brouwer serves on the Editorial Advisory Board for the Journal of Pharmaceutical Sciences and the Applied In Vitro Toxicology journal and is a reviewer for several additional journals. Dr. Brouwer is an adjunct faculty member in the Division of Molecular Pharmaceutics at the School of Pharmacy, University of North Carolina.

BO FENG, PHD, Vertex, Dr. Bo Feng is a Director in the Department of Drug Metabolism & Pharmacokinetics at Vertex Pharmaceuticals. She earned her Ph.D. from the Department of Pharmaceutical Sciences, 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, she joined Pfizer to lead a drug transporter group. In 2019, she joined Vertex Pharmaceuticals, and is leading the In vitro ADMET team. She continues to develop transporter and drug metabolizing enzyme strategies to support discovery and development portfolio. Her research interests include using transporter and metabolizing enzyme studies to develop in vitro to in vivo extrapolation and translational approaches to predict drug-drug interaction, toxicity, drug disposition and clearance. She has authored and coauthored over 60 original articles/reviews/book chapters and has given invited oral presentations at many scientific conferences.

KATHLEEN M. GIACOMINI, PHD, UCSF, Dr. Giacomini, a professor in the School of Pharmacy at the University of California, San Francisco, is a leader in the field of membrane transporters with a focus on genetic polymorphisms. She cloned, characterized and discovered the endogenous role of the human xenobiotic transporter, OCT1 (SLC22A1), and recently de-orphaned SLC22A24, an anion exchanger that preferentially transports steroid glucuronide conjugates. Together with others, she co-founded the International Transporter Consortium, which has published highly impactful papers informing regulatory policy. She is the Co-Principal Investigator of the UCSF-Stanford Center of Excellence in Regulatory Sciences and Innovation. She has received numerous awards including an honorary doctorate degree from Uppsala University, and is an elected member of the National Academy of Medicine.

MARCEL HOP, PHD, Genentech, Dr. Marcel Hop is Vice-President at Genentech and supervising the Drug Metabolism & Pharmacokinetics Department. He leads a team of about 80 scientists involved in acquisition and interpretation of ADME data in support of drug discovery and development ranging from early stage research to NDA and beyond. Before that, he was a Senior Director at Pfizer and a Senior Research Fellow at Merck. He has extensive experience in ADME sciences with a particular focus on PK optimization, human PK prediction, biotransformation, bioanalysis and, more recently, the use of in silico approaches and AI in drug discovery. He has authored more than 180 publications and made more than 80 external oral presentations. In addition, he co-authored one of the best-selling books in the ADME field: *Drug Metabolism and Pharmacokinetics Quick Guide*.

YURONG LAI, PHD, Gilead Sciences, Dr. Lai is a Sr. director of Drug Metabolism at Gilead Sciences. He is a fellow of American Association of Pharmaceutical Scientists and Adjunct Faculty in the Department of Pharmacy of the University of Rhode Island. His current role in Gilead is to lead DMPK strategies and implement in vitro/in vivo preclinical and clinical studies for compound advancement to regulatory filing. He received his M.D from Fujian Medical University in China and his Ph.D. (Toxicology) from Sapporo Medical University in Japan in 1998. Prior to joining Gilead Dr. Lai led research programs at Pfizer and BMS in transporter research and ADME-PK-Tox. He is the associate editor/editorial board member of top ranking DMPK journals including DMD, BDD, JPS and Frontier Pharmacology etc. He is a patent inventor and the author of a book, book chapters and over 150 original publications.

ALBERT P. LI, PHD, MBA, IVAL, Dr. Li has devoted his scientific career to the development and advancement of scientific concepts and in vitro technologies to accurately predict human drug properties including metabolic fate, drug-drug interaction potential, and organ-specific toxicity. His research is focused on the development and application of human-based in vitro experimental models, especially primary cultured human hepatocytes and, most recently, enterocytes, in the accurate assessment of human drug properties including metabolic fate, drug-drug interactions and drug toxicity. Dr. Li was one of the first scientists to successfully cryopreserve human hepatocytes, and recently further improved the technology to allow near perfection of human hepatocyte cryopreservation – 999Elite Cryopreserved Human Hepatocytes.

Dr. Li is currently President, CEO and co-founder of In Vitro ADMET Laboratories LLC, Columbia, MD and Malden, MA. He remains active in research, with >200 publications in peer-reviewed journals.

Previously, Dr. Li was President and CEO of Phase 1 Molecular Toxicology, Inc. in Santa Fe, New Mexico, U. S. A. (2002-2003), Chief Scientific Officer of In Vitro Technologies, Inc., Baltimore, Maryland, U. S. A. (1995-2002); Research Professor and Director of the Surgical Research Institute, Department of Surgery, St. Louis University Medical School (1993-1995); Senior Fellow and Director, Liver Biology Department, Monsanto Company (1982 – 1993); Group Leader, Cellular and Genetic Toxicology, Lovelace Inhalation Toxicology Research Institute (1979 – 1982); Assistant Professor and Research Scientist, Cancer Research and Treatment Center and Department of Radiology, University of New Mexico (1976 – 1979). Dr. Li obtained his B.

Sc. (1972, Chemistry) from the University of Wisconsin, Stevens Point, Ph. D. (1976, Biomedical Sciences) from the University of Tennessee, Oakridge Graduate School of Biomedical Sciences. His received his doctoral training and performed his dissertation research under Professor Abraham Hsie in the Biology Division of Oak Ridge National Laboratory, Oak Ridge, Tennessee, and MBA (2002) from the University of Maryland University College.

NA LI, PHD, C4 Therapeutics, Dr. Li is currently Senior Research Scientist in DMPK group at C4 Therapeutics. Prior to joining C4 Therapeutics, Dr. Li was a Principal Scientist in Pharmacokinetics and Drug Metabolism at Amgen Inc. As the functional lead of transporter group, her role was to drive transporter strategies to support Amgen drug discovery and development programs; establish in vitro to in vivo correlation related to drug transporter mediated absorption, distribution, and elimination to advance the science of human PK prediction and FIH dose projection. Dr. Li received her Ph.D. in Pharmacology from Dartmouth College in 2007. After graduation, she joined in Pfizer Global Research and Development to continue her postdoctoral research with Dr. Yurong Lai in translational science of transporter related ADME and PK-Tox. In 2009, she joined BD Biosciences, later acquired by Corning Life sciences. In 2017, she joined in Amgen. Dr. Li is a patent inventor and the author of more than 20 peer reviewed scientific publications.

IAIN MARTIN, PHD, Relay Therapeutics, Dr. Martin has been in the DMPK field for over 30 years and is currently Vice President of DMPK at Relay Therapeutics. Prior to his current role, he held positions at Merck, Schering Plough, Organon, AstraZeneca and The Upjohn Company, primarily supporting discovery programs and with a focus on understanding the structural and physicochemical determinants of DMPK behavior.

RANDY R. MILLER, Merck, After receiving a B.S. in Biochemistry at the Pennsylvania State University in 1987, Randy joined the Department of Drug Metabolism at Merck & Co., Inc., Rahway, NJ, U.S., where he is currently a Senior Principal Scientist. Over the past 30+ years he has been an active contributor and/or colead on numerous drug discovery and development teams spanning a wide range of pharmacological targets and has coauthored over 45 peer reviewed journal articles. In recent years, Randy has presented numerous internal and external lectures on the optimization of pharmacokinetics in drug discovery.

DAVID RODRIGUES, PHD, Pfizer, Dr. Rodrigues has been in the pharmaceutical industry for 31 years and currently holds the title of Senior Scientific Director as head of the Transporter Sciences Group at Pfizer (Groton, CT). Before joining Pfizer in 2014, he spent productive periods at Searle, Abbott Labs, Merck, and Bristol-Myers Squibb. During that time, he served on both scientific (Associate Research Fellow, Senior Research Fellow) and managerial (Director, Senior Director, Executive Director) ladders.

He has authored over a dozen book chapters, 171 peer-reviewed manuscripts, has presented at >80 venues (scientific symposia/meetings/webinars), and served on the editorial boards of various DMPK-related journals (e.g., *Current Drug Metabolism*, *Drug Metabolism Letters*, *Xenobiotica*, *Drug Metabolism & Disposition*). In addition, he has edited/co-edited three text books related to drug interactions and one on the topic of drug metabolism. Presently, he is a member of the International Transporter Consortium (ITC) and also serves as adjunct professor at the College of Pharmacy, University of Rhode Island. In 2009, David was inducted as Fellow of The American Association of Pharmaceutical Scientists (AAPS).

PÉTER TÁTRAI, PHD, SOLVO Biotechnology, Dr. Tátrai is a Senior Research Scientist at SOLVO. He graduated from the Eötvös University, Budapest, Hungary, in Cell and Developmental Biology, and did his PhD on extracellular matrix biology of chronic liver diseases and liver cancer at the Semmelweis University, Budapest. Following a brief involvement in molecular cancer diagnostics he moved to the Hungarian Academy of Sciences where he worked on the immortalisation and differentiation of

adipose-derived mesenchymal stem cells for experimental regenerative medicine. During a 3-year postdoctoral fellowship at the Cancer Research UK Cambridge Institute he studied mouse models of centrosomal disease. He joined Solvo in 2017, where he is responsible for product development as well as research collaborations.

MARK WENLOCK, PHD, Cyprotex, Dr. Wenlock was awarded a PhD in Organic Chemistry by the University of Cardiff, UK, in 1999. From there he went on to do post-doctoral work at Astra, UK, investigating the physicochemical properties that underpin successful oral drugs. He continued working as a drug discovery research scientist until 2015 at Astra and, later, AstraZeneca.

He became a specialist in the field of physical organic chemistry, in particular to small-molecule drug discovery. Building upon a thorough experimental foundation, Mark progressed into the area of applied artificial intelligence to ADME. Between 2009 and 2017, his principal focus was the use of automated work flows and machine-learning technologies in delivering in silico ADME predictions to support the drug-design process. In 2015, Mark established InSilicoLynx Ltd, which specialised in predictive ADME, developing tools to simplify the evaluation of compounds based upon dose and in vivo exposure for use at the virtual design and lead optimisation stages of drug discovery.

In 2017, Mark joined Cyprotex Ltd, UK, to lead the physical chemistry team. The team is responsible for the development and running of various low-throughput through to high-throughput equilibrium binding, lipophilicity and aqueous solubility assay variants. It consists of 18 physical chemists supporting high-quality physicochemical measurements that, to date, has seen demand increase nearly five-fold.

Mark has had over 20 papers published in peer-reviewed journals covering both in silico and in vitro areas of physical chemistry and DMPK, all underpinned by a passion to advocate for the application of physicochemical properties within early drug discovery.

BETH WILLIAMSON, PHD, AstraZeneca, Dr. Williamson graduated with a PhD in Pharmacology from the University of Liverpool, UK and began her career at Xenogesis, Nottingham before joining Vertex, Oxford and then leading a team in the DMPK group at Evotec, Oxford. Beth's work has focussed on DDIs and ADME assay optimisation and validation within drug discovery, particularly to address bespoke questions. Beth has published more than 15 papers and contributed to 2 book chapters (due to be published summer 2021). Beth is now part of the Early Oncology, DMPK group at AstraZeneca, representing DMPK on projects throughout discovery and development.

XIN XU, PHD, NCATS, Dr. Xin Xu is a Principal Investigator and Director of Pharmacokinetics at National Center for Advancing Translational Sciences (NCATS). Prior to joining NCATS, she had over 20 years of industrial experience in drug metabolism and pharmacokinetics. Dr. Xu has extensive experience in IND and NDA filings of novel therapeutics, ranging from small molecules to biologics, such as monoclonal antibody, nanobody, engineered human protein, protein-drug conjugate and gene therapy.

Dr. Xu obtained her B.Sc. degree from School of Pharmacy, Peking University Health Science Center, Beijing, China. She earned her Ph.D. degree in Pharmacokinetics from Faculty of Pharmacy, University of Toronto, where she also did her post-doctoral training in controlled release formulation. Dr. Xu has authored 242 publications (120 journal papers/ book chapters, and 122 conference presentations/abstracts). She is the co-inventor for five patents.

XINNING YANG, PHD, FDA, Dr. Xinning Yang is a Policy Lead in Guidance & Policy team (GPT) under the Office of Clinical Pharmacology (OCP), CDER of FDA. He received his Ph.D. in Pharmaceutical Science from University at Buffalo, mentored by

Dr. Marilyn Morris. In the past, as a clinical pharmacology reviewer, he reviewed a number of IND/NDA submissions contributing to the benefit/risk assessment of neurology drug products. His current primary focus is guidance and policy development and implementation in various areas, with more focus on drug metabolism, pharmacokinetics, and drug-drug interactions related Clinical Pharmacology issues. He is the Co-Chair of Transporter Focus Group of International Society of Studying Xenobiotics (ISSX) and a member of International Transporter Consortium (ITC) committee. He is participating in the International Council Harmonization (ICH) M12 DDI guidance global harmonization working group and serves as the Deputy Topic Lead. He published more than 20 peer-reviewed articles in journals and book chapters, made a number of presentations at different meetings, and also hosted/chaired symposiums or workshops at conferences.

ISMAEL ZAMORA, PHD, FDA, Dr. Zamora is CEO of Lead Molecular Design, S.L and associated professor at POMPEU Fabra University in Barcelona. He got the PhD in 1998 in the organic synthesis of natural projects, after 1 year postdoc with Professor Gabriele Cruciani at the University of Perugia, Italy working on modeling of ADME properties he joined AstraZeneca in Sweden at first as modeler for ADME properties inside of the DMPK department. He stayed at AstraZeneca for 3 years and contributed to the development of a global prediction system and to stablish the design groups between medicinal chemists, ADME scientists and modelers. In 2002, he founded Lead Molecular Design, S.L. in Barcelona, the company has been dedicated to develop new applications in the field of Medicinal Chemistry/ADME/Design such MetaSite, Shop, MassMetaSite, MassChemSite, WebChembase, Compound Library and WebMetabase in collaboration with Molecular Discover (distributor of the software developed www.moldiscovery.com). In 2010, Ismael Zamora received the Hansch award in QSAR and Modeling for the work done in the ADME area. Also, he has more than 50 articles and book chapters published in peer journals.

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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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SOLVO BIOTECHNOLOGY Since SOLVO's inception in 1999, our commitment to transporter research is still going strong, evidenced by a dedicated R&D team and 90+ peer reviewed publications to date. In addition to posters and publications, we gather thought leaders from industry and academia to present webinars and focused workshops on new transporter discoveries, provide invited lectures at conferences, and conduct one-to-one consultative discussions with small and large companies worldwide.

Whether you contract studies externally or perform your own research, it's important to have confidence in your resources. Partnering and collaborating with SOLVO brings you access to our in-depth expertise, our experience with regulatory-focused study design, and an ever-expanding portfolio of products and services to investigate transporter proteins and their impact on ADME/Tox. We invite you to talk with us to see how the experts at SOLVO can contribute to the success of your team.

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