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A BOSTON SOCIETY CONFERENCE

2020

WEBINAR

WEDNESDAY & THURSDAY, SEPTEMBER 16-17, 2020

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ORGANIZERS' WELCOME

Welcome to the 2020 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

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Conference Chair:
Steven Louie, BioIVT

Conference Chair-Elect:
Maria Fitzgerald, Sanofi

COMMITTEE MEMBERS
Heather Blanchette, Jnana Therapeutics
Dallas Bednarczyk, Novartis
Nimita Dave, Blueprint Medicines
Ruchia Duggal, Merck
Maria Fitzgerald, Sanofi
John S. Janiszewski, NIH/NCATS
Mitesh Patel, Novartis
Chris Rowbottom, Biogen
Wilson Shou, BMS
Ron Xu, ACEA Biosciences
Hui Zhang, Pfizer

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HT-ADME 2020 CONFERENCE AGENDA

DAY 1: WEDNESDAY, SEPTEMBER 16

SESSION I: ADME Prediction Tools for Old and New Technologies

10:00 - 10:05 AM	**Conference & Session Introduction** Steven Louie, BioIVT; Heather Blanchette, Jnana Therapeutics & Nimita Dave, Blueprint Medicines
10:05 - 10:35 AM	**Numerical Methods to Predict Drug-Drug Interactions Due to Time-Dependent Inactivation of Cytochrome P450s** Swati Nagar, Temple University
10:35 - 10:45 AM	**Q & A**
10:45 - 11:15 AM	**Alternative Approaches to Characterize in Vivo Clearance for Novel Modalities** Rob Foti, Merck
11:15 - 11:25 AM	**Q & A**
11:25 - 11:55 AM	**VENDOR PRESENTATION: IVAL** **999Elite Cryopreserved Human Hepatocytes for Drug Development** Albert Li, IVAL
11:55 - 12:00 PM	**Q & A**
12:00 - 1:00 PM	**LUNCH BREAK**

SESSION II: Transporter Mediated Drug Disposition

1:00 - 1:05 PM	**Session Introduction** Dallas Bednarczyk, Novartis & Wilson Shou, BMS
1:05 - 1:35 PM	**Inhibition of Folate Transport Pathways in Clinical Neural Tube Birth Defects** Maciej Zamek-Gliszczynki, GSK
1:35 - 1:45 PM	**Q & A**
1:45 - 2:15 PM	**Mechanistic Basis of Cabotegravir-Glucuronide Disposition in Humans** Mitesh Patel, Novartis
2:15 - 2:25 PM	**Q & A**
2:25 - 2:45 PM	**VENDOR PRESENTATION: Cyprotex** **Extreme High-throughput and Efficient Automated Workflow to Determine Blood to Plasma Ratio** Sravani Adusumalli, Cyprotex

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2:45 - 2:50 PM	**Q & A**

2:50 - 3:10 PM **VENDOR PRESENTATION: Sekisui XenoTech**
Lysosomal Trapping Studies to Evaluate Drug Distribution
Andrew G. Taylor, Sekisui XenoTech

3:10 - 3:15 PM **Q & A**

3:15 - 3:20 PM **Plenary Speaker Introduction**
Hui Zhang, Pfizer

3:20 - 4:00 PM **PLENARY:** **Transport-Mediated Drug Disposition: Tools to Assess and Methods to Translated Preclinical Data to Human**
Yurong Lai, Gilead

4:00 - 4:10 PM **Q & A**

DAY 2: THURSDAY, SEPTEMBER 17

SESSION III: Bioanalysis on New Therapeutic Modalities

10:00 - 10:05 AM **Conference & Session Introduction**
Maria Fitzgerald, Sanofi; Ruchia Duggal, Merck & John S. Janiszewski, NIH/NCATS

10:05 - 10:35 AM **DDI Considerations for Novel Therapeutics**
Chris Maclauchlin, Alnylam

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

10:45 - 11:15 AM **Hybridization LC-MS/MS of ASO in Plasma and Brain Tissue**
Pei Li, Biogen

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

11:25 - 11:55 AM **RAPID - A High-throughput, Cell-based Drug Discovery Platform for SLC Transporters**
Justin Rettenmaier, Jnana Therapeutics

11:55 - 12:05 PM **Q & A**

12:05 - 12:25 PM **VENDOR PRESENTATION:**
Investigating Drug Transport and Potential DDI's Using Multi-Transporter Models
Mark Warren, BioIVT

12:25 - 12:30 PM **Q & A**

12:30 - 1:30 PM **LUNCH BREAK**

| 1:30 - 2:00 PM | **Re-thinking High Throughput ADME Screening: Implementation of Routine High-Performance Micro-Flow LC-MS/MS Analysis in Early Discovery"** |
| | Brendon Kapinos, Pfizer |

| 2:00 - 2:10 PM | **Q & A** |

SESSION IV: New Clearance Prediction Models

| 2:10 - 2:15 PM | **Session Introduction** |
| | Mitesh Patel, Novartis |

| 2:15 - 2:45 PM | **HCS Imaging Approaches in Safety** |
| | Joe Trask, PerkinElmer |

| 2:45 - 2:55 PM | **Q & A** |

| 2:55 - 3:00 PM | **Plenary Speaker Introduction** |
| | Steven Louie, BioIVT |

| 3:00 - 3:40 PM | **PLENARY:** **Renal Impairment: Simulation-based Analysis of Determinants of Clearance** |
| | Marilyn Morris, Univ. of Buffalo |

| 3:40 - 3:50 PM | **Q & A** |

| 3:50 - 3:55 PM | **CLOSING REMARKS** |
| | Maria Fitzgerald, Sanofi |

ABSTRACTS

SESSION I

Numerical Methods to Predict Drug-drug Interactions Due to Time-dependent Inactivation of Cytochrome P450s
Swati Nagar, Temple University

Cytochrome P450 (CYP) enzyme kinetics often do not conform to Michaelis-Menten assumptions, and time-dependent inactivation (TDI) of CYPs displays complexities such as multiple substrate binding, partial inactivation, quasi-irreversible inactivation, and sequential metabolism. In vitro experimental considerations such as lipid partitioning, enzyme concentrations, and inactivator depletion are additional complexities that must be considered. Numerical approaches using ordinary differential equations of the kinetic schemes offer several advantages over the traditional replot method used to analyze in vitro TDI datasets. Improvement in the parameterization of CYP in vitro kinetics has the potential to improve prediction of clinical drug-drug interactions (DDIs). The extrapolation of CYP in vitro TDI parameters to predict in vivo DDIs is discussed, along with a discussion on current gaps in knowledge and future directions to improve the prediction of DDI with in vitro data for CYP catalyzed drug metabolism.

Alternative Approaches to Characterize In Vivo Clearance for Novel Modalities
Rob Foti, Merck

Drug discovery efforts have rapidly undergone a transformational shift from being focused mainly on small molecules to encompassing an ever expanding array of novel modalities including small molecules, antibodies, engineered proteins, oligonucleotides and gene-based therapies. While a host of well-characterized in vitro and in silico approaches are routinely applied to triage small molecule drug candidates, characterizing the pharmacokinetic properties of many novel therapeutic modalities still requires a strong dependence on

in vivo studies. This talk will describe an integrated approach towards reducing the number of preclinical studies for a series of peptide-antibody conjugates by incorporating molecular charge, hydrophobic interaction chromatography, and FcRn binding affinity. A novel in vitro approach using cryopreserved hepatocytes to predict the in vivo clearance of the antibody conjugates in preclinical species will be described. While such approaches will ultimately need to be evaluated on a modality-by-modality basis, the concepts discussed will provide additional tools for rapidly advancing novel therapeutic modalities.

SESSION II

Inhibition of Folate Transport Pathways in Clinical Neural Tube Birth Defects
Maciej J. Zamek-Gliszczynski, GlaxoSmithKline

Preliminary analysis of ongoing birth surveillance study identified evidence of potential increased risk for neural-tube defects (NTDs) in newborns associated with exposure to dolutegravir at time of conception (Zash et al. 2008). Folate deficiency is a common cause of NTDs. Folate's hydrophilic nature results in negligible passive membrane permeability and transport-mediated disposition. Dolutegravir and other HIV integrase inhibitor drugs were evaluated for inhibition of folate transport pathways: proton-coupled folate transporter (PCFT), reduced folate carrier (RFC), and folate receptor α (FRα)-mediated endocytosis (Zamek-Gliszczynski et al., 2019). Inhibition of folate transport was extrapolated to clinic using established approaches for transporters in intestine, distribution tissues, basolateral and apical membranes of renal proximal tubules (2017 FDA Guidance). The present studies showed that dolutegravir is not a clinical inhibitor of folate transport pathways, and it is not predicted to elicit clinical decreases in maternal and fetal folate levels. Furthermore, clinically-relevant HIV integrase inhibitor drug class effect on folate transport pathways was not observed.

Consistent with these findings, upon more complete enrollment of the birth surveillance study, dolutegravir no longer exhibited increased risk for NTDs (Zash et al., 2020).

Mechanistic Basis of Cabotegravir-Glucuronide Disposition in Humans
Mitesh Patel, Novartis

Cabotegravir, a novel HIV integrase inhibitor, is primarily metabolized by UGT1A1 and UGT1A9 to a direct ether glucuronide metabolite. Cabotegravir glucuronidation was predominantly hepatic (>95%) with minimal intestinal and renal contribution. Cabotegravir-glucuronide biliary excretion was mediated by multidrug resistance-associated protein MRP2, whereas hepatic basolateral excretion into sinusoidal blood was via both MRP3 [fraction transport (Ft) = 0.81] and MRP4 (Ft = 0.19). Surprisingly, despite high urinary recovery of hepatically-formed cabotegravir-glucuronide, metabolite levels in circulation were negligible, a phenomenon consistent with rapid metabolite clearance. Cabotegravir-glucuronide was transported by hepatic uptake transporters OATP1Bs; however, metabolite clearance by hepatic uptake from circulation was low (2.7% of hepatic blood flow) and unable to explain the minimal systemic exposure. Instead, circulating cabotegravir-glucuronide undergoes efficient renal clearance, where uptake into the proximal tubule is mediated by OAT3, and subsequent secretion into urine by MRP2 (Ft = 0.66) and MRP4 (Ft = 0.34). These studies provide mechanistic insight into the disposition of cabotegravir-glucuronide, a hepatically-formed metabolite with appreciable urinary recovery and minimal systemic exposure.

VENDOR PRESENTATION

Extreme High-throughput and Efficient Automated Workflow to Determine Blood to Plasma Ratio
Sravani Adusumalli, Cyprotex

The blood to plasma ratio determines the concentration of a compound in plasma and erythrocytes. The knowledge of red blood cell partitioning is an important parameter in drug discovery and development in elucidating pharmacokinetic profile of the compounds. The value of blood to plasma ratio gives an important estimate in predicting the drug's clearance. Different methods are available to determine the blood to plasma ratio of compounds which are low throughput, laborious and time consuming. A literature survey revealed that currently there is no high-throughput approach developed. We developed a high throughput technique adapted from method developed by Saha et al (Mass Spectrom Purif Tech 2017) utilizing plasma fractions obtained from whole blood to back calculate the binding of drug to erythrocytes. The technique facilitates running 96 compounds (n=4) in 384 well plate requiring one scientist and half a day to run the assay. The goal of this talk is to describe a highly automated and high throughput method developed in 384 well plate to determine the blood to plasma ratio which significantly lowers labor, time and cost in comparison to current available methods. This high throughput screening method makes it easy for adoption of the assay forroutine screening in early drug development to screen large number of compounds efficiently.

VENDOR PRESENTATION

Lysosomal Trapping Studies to Evaluate Drug Distribution
Andrew G. Taylor, Sekisui XenoTech

The physicochemical properties of a drug have a large determination on the likelihood for the drug to become trapped within lysosomes. Lipophilic or amphiphilic drug candidates with ionizable amines have the strongest potential to fall victim to lysosomal trapping. While lipophilic amine drugs readily diffuse across cell membranes at physiological pH, upon diffusion into the acidic environment within lysosomes these compounds become protonated, thus preventing their diffusion back into the cytosolic space. This process can result in large organ-to-blood distributions of the drug that may be mistaken for active transport. Additionally, sequestration of these compounds within lysosomal bodies can potentially be a mechanism of other types of drug-drug interactions (DDIs). Several assays are available to investigate

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a drug's potential for lysosomal trapping, and data derived from these experiments can help the drug developer assess risk impacted by pharmacokinetics, DDIs, and other safety parameters. This presentation will cover:

- An overview of lysosomes
- The mechanism of lysosomal trapping
- Lysosomal trapping and drug-drug interaction (DDI) potential
- Direct and indirect study design elements and important considerations
- Appropriate test system options for lysosomal trapping studies

PLENARY

Transport-Mediated Drug Disposition: Tools to Assess and Methods to Translated Preclinical Data to Human
Yurong Lai, Gilead

The extended clearance concept (ECC) that incorporates the processes of hepatic transport, metabolism and biliary excretion is the current approach thought to be able to estimate the total clearance for drug candidates that undergo transporter-mediated clearance; However, the equation can be misused for selecting compounds in the drug discovery phase due to the inability in predicting human PK profile and often under-estimating T1/2. Therefore, when human clinical data is not available in the drug discovery phase, a mechanistic PBPK model that is fully validated in probe animals is needed for scaling factors (SFs) of IVIVC, and the SFs obtained from the probe animals can be used for constructing human PBPK models to prospectively predict human PK. This presentation is formulated to answer questions on "why" and "how" in developing and validating a PBPK model in probe animals. The case examples will be discussed.

SESSION III

DDI Considerations for Novel Therapeutics
Chris Maclauchlin, Alnylam

N-acetylgalactosamine (GalNAc)- small interfering RNAs (siRNAs) are synthetic, chemically modified, double stranded RNA molecules conjugated to a triantennary N-acetylgalactosamine ligand to facilitate preferential delivery to the liver. GalNAc siRNAs are smaller (~16,000 Da) than biologic therapeutics (>150,000 Da) but much larger than typical small drug molecules (<900 Da). Regulatory agencies provide no recommendations for oligonucleotide therapeutics including siRNAs; therefore, small molecule guidance documents have historically been applied. Standardized DDI assays have been useful in extrapolating in vitro data to in vivo clinical risk. Over ~10 years, comprehensive in vitro DDI investigations with GalNAc- siRNAs have been conducted during nonclinical drug development to assess the clinical DDI potential as substrates, inhibitors, or inducers of major cytochrome P450s (P450s) and as substrates and inhibitors of transporters. The cumulative analysis of these data across a platform of GalNAc-siRNA molecules demonstrates that, like new biological entities, these oligonucleotide-based therapeutic drugs are unlikely to result in pharmacokinetic DDIs; therefore, the need for in vitro or clinical investigations are unlikely to yield useful information.

Hybridization LC-MS/MS of ASO in Plasma and Brain Tissue
Pei Li, Biogen

Quantitative bioanalysis in plasma and tissues samples are required to study the pharmacokinetic and pharmacodynamic properties of antisense oligonucleotides (ASOs). To overcome intrinsic drawbacks in specificity, sensitivity and throughput of traditional ligand-binding assay (LBA) and LC-MS/MS methods, an alternative bioanalytical method was developed by combining oligonucleotide hybridization and LC-MS/MS technologies. Target ASOs were extracted from biological samples by hybridization with biotinylated sense-strand oligonucleotides coupled to streptavidin magnetic beads. Using ion pairing chromatography and tandem

mass spectrometry (MS/MS), this method demonstrated high sensitivity (0.5 ng/mL using 100 μL of plasma), high specificity, wide linear range, complete automation and generic applications in tests with multiple ASOs. The typical challenge of sensitivity drop in traditional ion-pairing LC-MS/MS was for the first time overcome by the introduction of a ternary pump system. Due to the high specificity, quantitation in various biological matrices was achieved using calibration standards in plasma, largely improving efficiency and consistency. Another major advantage was the capability of simultaneous quantitation of ASO metabolites. The hybridization LC-MS/MS was considered an improved alternative for quantitation of ASOs and metabolites in plasma and tissue samples, showing a great potential to replace traditional LBA and LC-MS/MS methods.

RAPID - A High-throughput, Cell-based Drug Discovery Platform for SLC Transporters
Justin Rettenmaier, Jnana Therapeutics

The solute carrier (SLC) transporter family is the largest group of metabolite transport proteins in the body, accounting for about 2% of known human coding genes. SLC transporters move metabolites across cell membranes, for the precise control of metabolite levels within cells, tissues and organs for healthy cellular metabolism. Despite their central role in human physiology, fewer than 20 of the 450 SLC transporters are targeted by approved drugs — underscoring a massive untapped therapeutic opportunity. Despite their immense promise, SLCs are often considered to be intractable targets for hit generation and lead discovery, due to the difficulty of working with these multipass transmembrane proteins and the lack of pre-defined assay technologies to enable their study. To address this challenge, Jnana has built a proprietary ligand discovery platform called Reactive Affinity Probe Interaction Discovery (RAPID) that is carried out in live cells, where SLCs are present in their native membrane environment. RAPID is a 'plug-and-play' technology that identifies small-molecule binders irrespective of the fold or function of the target protein, delivering high quality, chemical matter for targets of interest. RAPID is ideally suited for SLC transporters which are highly diverse based

on structure and cellular location, often difficult to express and purify, are not readily amenable to biophysical methods, and may have no known ligands. Jnana is using our RAPID platform to advance drug-discovery programs in our internal pipeline and in collaborations with biopharma partners to systematically target SLC transporters and develop small molecule therapeutics to treat a wide range of diseases.

VENDOR PRESENTATION

"Investigating Drug Transport and Potential DDIs Using Multi-Transporter Models
Mark Warren, BioIVT

In vivo drug movement is often regulated by multiple transporter interactions. Simple in vitro uptake or efflux transporter models can provide critical information about the effects of a compound on specific transporters; however, these models cannot always account for interaction effects. The presentation will outline how OPTI-EXPRESSION™ Technology is used to transfect cells with multiple transporters. Multi-transporter models will be illustrated using published research that demonstrates improved IVIVC versus conventional systems and be used to better predict the ADME profile of drug candidates.

Re-thinking High-Throughput ADME Screening: Implementation of Routine High-Performance Micro-Flow LC-MS/MS Analysis in Early Drug Discovery
Brendon Kapinos, Pfizer

High-throughput ADME screening drives preclinical pharmacokinetic assessment and optimization in modern biopharmaceutical drug discovery. Automated liquid-handling workstations programmed with 96-and 384-well plate-based in vitro assays can generate thousands of samples from a single study, and high-throughput LC-MS/MS techniques usually rely on high LC (1-2mL/min) to deliver maximum throughput. However, these workflows require costly consumables for assay execution (plates, tips, reagents), liters of LC-MS/MS mobile phase per run, and generate substantial hazardous waste. Herein we describe development of a high-throughput, micro-flow

LC-MS/MS method and application toward a model screen cassetted shake-flask LogD (SFLogD) to drastically reduce cost and hazardous waste generated while increasing assay performance. Compound cassetting resulted in identical effective throughput (15s/injection/compound) and enhanced analytical performance to previously-established high-flow methods.

SESSION IV

HCS Imaging Approaches in Safety
Joe Trask, PerkinElmer

The emergence of new in vitro based cell models to resemble and recapitulate responses similar to in vivo has slowly expanded into preclinical safety and toxicological studies. Validation of these models is critical for repeatability of these assays to predict outcomes. High content screening (HCS) imaging is a technological that provides a non-biased approach of automated microscopy to identify proteins and many phenotypic morphological features that can use machine learning strategies for detection and post data analysis. HCS imaging has evolved in toxicology programs since first being used to identify micronuclei in genotoxicity studies to now measure other hepatotoxicity markers, cholestasis, phospholipidosis, steatosis, and other phenotypic characteristics of cells. In this talk, I will discuss the emerging in vitro cell models such as co-cultures, 3D spheres, and organ on a chip models that are amenable for HCS imaging and a few insights comparisons with known reference compounds and remaining challenges and solutions.

PLENARY

Renal Impairment: Simulation-based Analysis of Determinants of Clearance
Marilyn E. Morris, University of Buffalo

Renal impairment (RI) is a major health concern both in the United States and globally, with the prevalence of chronic kidney disease affecting over 25 million adults in the US. While RI significantly impacts the clearance of drugs through changes in glomerular filtration rate, other changes including alterations in protein binding, in the expression of renal drug transport proteins and hepatic metabolizing enzymes and in toxin-drug interactions may also contribute to alterations in drug pharmacokinetics (PK). We have utilized physiologically based PK modeling incorporating in vitro and in vivo (preclinical and clinical) data to assess changes in renal and total clearances for drugs undergoing active renal reabsorption, active secretion, and for drugs eliminated predominantly by hepatic metabolism. This presentation will share our use of simulations with in vitro and preclinical/clinical data, in order to quantitatively predict the importance of changes in protein binding, transporter/metabolizing enzyme expression and activity in RI patients. The quantitative characterization of the effects of RI on PK is of vital importance to provide predictions for proper dosing of medications involved in RI, and with the disease states associated with RI. This research highlights the importance of understanding the impact of RI on clearance on a mechanistic level.

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SPEAKER BIOGRAPHIES

SRAVANI ADUSUMALLI, PHD, Cyprotex, Dr. Adusumalli graduated from University of Rhode Island with a PhD in Pharmaceutical Sciences in 2017. During her PhD program she was working on many ambitious projects in collaboration with Pfizer and National Institute on Alcohol Abuse and Alcoholism. She is currently a Senior Scientist at Cyprotex, an Evotec Company. There she designs and executes ADME studies for discovery and development stage compounds including cell based or biochemical assays.

ROBERT S. FOTI, PHD, Merck, Dr. Foti is a Senior Principal Scientist at Merck (Boston, MA) where he leads drug disposition efforts for small molecule and protein therapeutics across multiple therapeutic areas. Prior to joining Merck, Rob held positions at Amgen, Inc. (Cambridge, MA), leading the in vitro ADME group and supporting multi-modality drug discovery and development efforts across the neuroscience, oncology and inflammation portfolios and at Pfizer (Groton, CT), contributing to discovery ADME efforts and high-throughput screening assays to assess metabolic stability and drug interactions. He received his undergraduate degree in Chemical Biology from Stevens Institute of Technology (Hoboken, NJ), his masters in Chemistry from Lehigh University (Bethlehem, PA) and his Ph.D. in Molecular Pharmacology from the University of Nice – Sophia Antipolis (Nice, France). The current research in Rob's lab focuses on the assessment of clearance and biodistribution mechanisms for both small molecules and protein therapeutics. Additional research interests include cytochrome P450 and UGT enzymology, drug distribution and drug target characterization, resulting in nearly 50 peer-reviewed manuscripts, book chapters and invited reviews. Externally, Rob is on the Editorial Board for Drug Metabolism and Disposition and Drug Metabolism Letters, is the current Chair-Elect for the Drug Metabolism and Disposition Division of ASPET and is an active member of ISSX and SEBM while contributing as an ad hoc referee for multiple peer-reviewed journals.

BRENDON KAPINOS, Pfizer, Brendon Kapinos is a Senior Scientist in Hit Discovery and Optimization (HDO) at Pfizer in Groton, Connecticut and oversees the group's high-throughput bioanalytical operations. He joined Pfizer in 2007 after obtaining a B.S in Biotechnology from the Rochester Institute of Technology, and accepted a position in the department of Pharmacokinetics, Dynamics and Metabolism. He later joined HDO, developing high-throughput in vitro ADME screens, LC-MS/MS platforms and workflows while completing his M.A in Biology from Brown University. Brendon is a member of the American Society for Mass Spectrometry and has presented on high-throughput LC-MS/MS technologies, as well as development and applications of micro-flow LC-MS/MS.

YURONG LAI, PHD, Gilead, 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.

PEI LI, PHD, Biogen, Dr Li is a scientist in the Drug Metabolism and Pharmacokinetics Department of Biogen Inc. (MA, USA). Pei obtained his BS degree in Biological Sciences from Nanjing University (China) and his PhD degree in Biomedical and Pharmaceutics Sciences from the University of Georgia (GA, USA). After spending 4 years as a bioanalytical team leader in clinical drug testing and CRO environments, he joined his current department at Biogen in 2018. Pei's expertise lies in quantitative LC–MS bioanalysis of small molecule drugs, proteins and oligonucleotides in complex biological matrices. His experience also covers regulated bioanalysis for the support of preclinical and clinical drug development.

CHRISTOPHER MACLAUCHLIN, PHD, Alnylam Pharmaceuticals, Dr MacLauchlin is a Director of DMPK at Alnylam Pharmaceuticals, Inc., a pharmaceutical company focused on developing innovative RNAi-based medicines. Chris has approximately 20 years of research and development experience and has had positions of increasing responsibility in diverse organizations in the pharmaceutical and biotechnology sector. He has a broad range of expertise in understanding drug disposition and has worked on numerous approved products. At Alnylam, Chris provides DMPK guidance to programs to support portfolio development. He had a central role in ensuring the DMPK components were complete and authored regulatory components in support of the NDA/MAA filing of Patisiran and Lumasiran.

Chris obtained a Ph.D. in Medicinal Chemistry at the University of North Carolina at Chapel Hill. Chris began his career in industry at Magellan Laboratories/Cardinal Health (Raleigh, NC), in their Drug Metabolism group. In 2003 he joined GlaxoSmithKline (RTP, NC) in the DMPK Mechanism and Extrapolation Technology (MET) group where he remained for 12 years. He specialized in metabolism and disposition properties of development compounds to identify liabilities and provide guidance to manage those liabilities in the clinic. In addition, Chris provided DMPK representation on project teams in the development of numerous metabolic, oncology and anti-infective drug candidates from candidate selection through Phase IV. In 2015 Chris joined Cempra,

Inc, a biotech focused on development of a new macrolide anti-biotic as a director of clinical programs. While there he used his experience in DMPK to provide interpretive guidance for strategic decision making critical for safety, marketability and regulatory requirements including the writing of key regulatory documents for NDA and MAA submission for Solithromycin.

MARILYN MORRIS, PHD, University of Buffalo, Dr. Morris is SUNY Distinguished Professor and Chair in the Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences University at Buffalo, State University of New York (SUNY). Her research focuses on the influence of drug transporters on drug pharmacokinetics and pharmacodynamics and the identification of transporters as therapeutic targets. She is a Fellow of AAPS, as well as the American Association for the Advancement of Science, and recipient of the SUNY Chancellor's Award for Excellence in Research, AAPS National Biotechnology Conference Innovations in Biotechnology Award (2015), AAPS Research Achievement Award in PPDM (2016) and AAPS Distinguished Service Award (2018). She is a past AAPS President, and currently serves as an elected member of the International Pharmaceutical Federation's Board of Pharmaceutical Sciences, as well as a member of the NIH XNDA study section. She has published 185 peer-reviewed publications, 15 book chapters and is the co-editor of the book "Drug Transporters:Molecular Characterization and Role in Drug Disposition", and Associate Editor of AAPS J. Dr. Morris has served as the major advisor of 32 PhD students and 19 M.S., and many Pharm.D. and undergraduate students, and previously served as Associate Dean of the Graduate School at the University at Buffalo.

SWATI NAGAR, PHD, Temple University, Dr. Swati Nagar is a Professor in the Department of Pharmaceutical Sciences at Temple University School of Pharmacy. She obtained her Ph.D. in Pharmaceutics at the University of Minnesota in 2003. She completed a postdoctoral fellowship in Pharmacology at Fox Chase Cancer Center in 2005. Swati joined Temple University School of Pharmacy, Department of Pharmaceutical Sciences in 2005 as Assistant Professor, and was promoted to the rank of Associate Professor with tenure in 2011, and Professor in 2018. She teaches Pharm D and graduate pharmacokinetics. Her lab has a long-standing interest in understanding the disposition of conjugated metabolites, specifically the pharmacokinetics of metabolites with respect to their formation and transport. Further, in collaboration with Dr. Ken Korzekwa, she is developing methods to better understand complex kinetics of time-dependent inhibition toward improved clinical drug-drug interactions. Another key collaborative area of research with the Korzekwa lab is developing models to predict intracellular concentrations in the presence of drug transporters, with a focus on membrane partitioning and permeability of drugs.

Swati has co-authored 55 peer-reviewed research and review articles, and she co-edited a book titled 'Enzyme Kinetics in Drug Metabolism: Fundamentals and Applications' published in 2014 (Springer/Humana Press). Swati is a past Chair of the Delaware Valley Drug Metabolism Discussion Group, past Chair of the AAPS PPDM Drug Metabolism Focus Group, and Chair of the 2018 Gordon Research Conference on Drug Metabolism. She currently serves on the editorial board of Drug Metabolism and Disposition and Xenobiotica.

MITESH PATEL, PHD, Novartis, Mitesh Patel received a BSc in Pharmacy from University of Mumbai, India and a Ph.D. in Pharmaceutical Sciences from University of Missouri-Kansas City, Missouri. He then obtained his Postdoctoral training at GlaxoSmithKline where he investigated transporter-mediated drug disposition to provide mechanistic basis for their unusual clinical PK. Dr. Patel has previously worked as a PKDM Scientist at Amgen where he mainly focused on designing, executing, interpreting, and contextualizing appropriate transporter studies to explain uncharacteristic drug PK for small molecule drugs. At present, he is working as a Principal Scientist in the Department of Pharmacokinetic Sciences at the Novartis Institutes for Biomedical Research in Cambridge, Massachusetts. During his years of employment, he has served as a subject matter expert on transporter-mediated drug absorption, distribution, excretion, DDIs.

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JUSTIN RETTENMAIER, PHD, Jnana Therapeutics, Dr. Rettenmaier is an Associate Director in Chemical Biology at Jnana Therapeutics. While at Jnana, he co-invented the RAPID ligand discovery technology, which for the first time enables the high-throughput and systematic identification of lead-like small molecules that bind to SLCs in their native cellular environment. In addition to his role in further development of the RAPID technology, Justin also leads efforts to validate novel targets across a range of immune-mediated diseases. Prior to Jnana, Justin conducted postdoctoral research in the laboratory of the late Susan Lindquist at the Whitehead Institute, where he focused on the identification of novel targets for the treatment of neurodegenerative disease. He obtained his PhD in Chemical Biology at UCSF under the supervision of Jim Wells, where he focused on the identification of allosteric activators of protein kinases as well as developing technologies to enable fragment-based ligand discovery against challenging targets.

ANDREW G. TAYLOR, PHD, SEKISUI XenoTech, Dr. Andrew G. Taylor serves as the Technical Support Manager for Services at SEKISUI XenoTech. Dr. Taylor received his Ph.D. from the University of California, San Diego/Scripps Institution in 2014 and joined SEKISUI XenoTech in 2017 as a Study Director specializing in drug transporter and drug metabolism studies. As a contract service specialist, Andrew serves clients pursuing NDA or IND submission. More specifically, he facilitates solutions to ADME and drug-drug interaction (DDI) challenges with appropriate in vitro and in vivo studies, ensuring experimental designs and data reports meet the clients' needs and—most importantly—satisfy requirements set forth by the regulatory agencies. His experience as a study director lends specialized insight into the technical aspects of ADME/DDI preclinical work, and his role in facilitating client success gives him the ability to provide context and meaning for these studies.

JOE TRASK, PerkinElmer, Joe Trask is a Principal Product Scientist in the Cellular Imaging and Analysis group at PerkinElmer. He is instrumental in strategic customer support through teaching, training, and collaborations. He brings over 20 years of experience in high content screening technology from academia (Duke University and The Ohio State University), pharmaceutical industry (Abbott Laboratories and Sphinx Laboratories, Division of Eli Lilly & Company), and biotechnology (The Hamner Institute for Health Sciences and ScitoVation LLC). Joe has extensive experience in cell based technologies from flow cytometry, confocal microscopy and computer-assisted automated microscopy studying cancer, immunology, neurodegeneration, and toxicology. Joe has published several research articles and book chapters in High Content Imaging field. Joe is an associated editor for the NIH/NCATS Assay Guidance Manual and was a co-founder and first President of Society for Biomolecular Imaging and Informatics (SBI2).

MARK WARREN, PHD, BioIVT, Dr. Mark Warren serves as the Senior Director, Transporter Assay Services at BioIVT where he helps clients design and implement transporter research programs. He has led more than 1,000 IND-enabling or NDA-enabling transporter studies for numerous companies, and conducted hundreds of mechanistic studies. Previously, Mark was a Principle Investigator at XenoPort, Inc. from 2002-2010, where he worked on early- stage discovery and development of NCEs that took advantage of human transporters to improve absorption and PK properties over those of existing medications. His studies included investigations of gabapentin enacarbil, which was approved by the FDA in 2011. Prior to that, Mark worked at Microcide, Inc., from 1996-2002 on early stage discovery of inhibitors of bacterial efflux transporters that are responsible for antibiotic resistance. Mark received his B.S in Genetics from UC Davis, his M.S in Chemistry from UC San Diego and his Ph.D. in Chemistry and Biochemistry from UC San Diego.

MACIEJ J. ZAMEK-GLISZCZYNSKI, PHD, GlaxoSmithKline, Dr. Zamek-Gliszczynski has 15 years of industry (Eli Lilly and GSK) experience in leading DMPK and PK/PD/clinical pharmacology aspects of oncology, endocrine/metabolic, and infectious disease programs at all stages between discovery, clinical development, and post-marketing (6 clinical candidate selections & INDs, 2 NDAs). He is an experienced global manager, having led the Quantitative Drug Disposition group responsible for understanding victim and perpetrator DDIs for the entire GSK portfolio. Dr. Zamek-Gliszczynski's research is focused on PK/PD and DDI implications of drug and metabolite transport. He is the author of >100 manuscripts and presentations on this subject (>5,000 cites, h¬-index = 35). 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 PK/PD/Drug Metabolism (PPDM) section, and he served as GSK management representative on IQ Translational ADME Leadership Group (TALG). He has been active in organizing DMPK/clinical pharmacology meetings with ITC, ASCPT and AAPS. 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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