

Institute
for
Scientific
Communications

DDI-2017

20th Anniversary of the International Conference on Drug-Drug Interactions:

Pioneer Symposium: Key Scientific Concepts and technical Approaches; Regulatory Perspectives and Clinical Practice; Extended Clearance Concept on Drug Interactions; Drug Metabolites as Contributors to Drug Interactions; Drug-transporter Interactions; Enzyme Induction and Nuclear Receptors; Novel Approaches in Drug Interactions; Biologics-Drug Interactions

June 19 – 21, 2017

Husky Union Building, University of Washington; Seattle, WA, USA
4001 NE Stevens Way, Seattle, WA 98195
(206) 543-8131

REGISTRATION DISCOUNT UNTIL MAY 20, 2017

ISC, INC.

9221 Rumsey Road, Suite # 8
Columbia, Maryland 21045 USA



DDI-2017 MEDIA PARTNER

Featuring the Following Experts: Ken Thummel; Leslie Benet; Kim Brouwer; Brian Houston; Yuichi Sugiyama; Larry Wienkers; Albert Li; Isabelle Ragueneau-Majlessi; Phil Hansten; John Horn; Lei Zhang; Jashvant Unadkat; Ayman El-Kattan; Mathena Varma; Ken Grime; Niresh Hariparsad; Jan Wahlstrom; Nina Isoherranen; Bo Feng; Kenneth Brouwer; Robert Foti; Yurong Lai; Jane Kenny; Julia Cui; Li Di; Theunis Goosen; Jialin Mao; Yuan Chen; Elimika Fletcher; Pratap Singh; Stephen Wang; Nagendra Chemuturi.

DDI-2017 is a yearly event providing a comprehensive update on the status of the science of drug-drug interactions and its relevance to drug development. The conference will include a review on the current status of DDI potential of biologics, industrial perspectives and other relevant topics.

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Organizing Chairs:

Albert P. Li, APSciences/In Vitro ADMET Laboratories, Inc.
Isabelle Ragueneau-Majlessi, University of Washington
Jashvant Unadkat, University of Washington
Kenneth Brouwer, Qualyst Transporter Solutions, LLC
Jane Kenny, Genentech
Theunis Goosen, Pfizer, Inc.
Jan Wahlstrom, Amgen Inc.
Stephen Wang, Pfizer, Inc.

DDI-2017
20th Anniversary:
International Conference on Drug-Drug
Interactions

MONDAY, JUNE 19, 2017
DDI-2017 – DAY 1

7:00 AM – 8:00 AM – REGISTRATION

8:00 AM – 8:15 AM

Welcome Remarks: Albert P. Li, APSciences/IVAL

8:15 AM – 8:45 AM

Opening Remarks (Ken Thummel, University of Washington; Seattle, WA)

Session 1: Pioneer Symposium: Key Scientific
Concepts and Technical Approaches
(Chair: Albert P. Li)

8:45 AM – 9:15 AM

Biopharmaceutics Drug Disposition Classification System (BDDCS) and Drug-Drug Interactions (Leslie Z. Benet, University of California San Francisco; San Francisco, CA) The purpose of BDDCS is to predict drug disposition and potential drug-drug interactions in the intestine and the liver, and potentially the kidney and the brain. For drugs on the market BDDCS may be used to: predict potential drug-drug interactions not tested in the drug approval process; predict the potential relevance of transporter-enzyme interplay; assist the prediction of when and when not transporter and/or enzyme pharmacogenetic variants may be clinically relevant; predict when transporter inhibition of uremic toxins may change hepatic elimination; predict the brain disposition of drugs; and increase the eligibility of drugs for BCS Class 1 biowaivers using measures of metabolism. For NMEs the use of BDDCS and its role in drug development encompass: prediction of the major route of elimination for an NME in humans (metabolisms vs excretion of unchanged drug in the urine and bile); prediction of the relevance of transporters and transporter-enzyme interplay in drug disposition as described for drugs on the market; prediction of central or lack of central effects; and prediction of the effects of high fat meals on the extent of bioavailability.

9:15 AM – 9:45 AM

Hepatic Efflux Transporters: Relevance to Drug-Drug Interactions and Drug Toxicity (Kim Brouwer, The University

of North Carolina at Chapel Hill; Chapel Hill, NC) Efflux transporters located on the basolateral and apical membranes of hepatocytes play an important role in the systemic disposition and hepatic excretion of many endogenous and exogenous compounds, including bile acids, drugs and metabolites. Disease-mediated and drug-induced alterations in hepatic efflux transporters may impact drug efficacy and/or toxicity. The interplay between bile acid exposure, hepatic transporter dynamics, and the regulation of these proteins will be discussed. Innovative *in vitro* and *in vivo* tools to evaluate how drug interactions and disease influence the function of these proteins, and modeling approaches to improve predictions of hepatic transporter-mediated drug interactions and bile acid-mediated drug-induced liver injury, will be presented.

9:45 AM – 10:15 AM – BREAK

10:15 AM – 10:45 AM

Assessment of Transporter-mediated Drug-drug Interactions: Implications of Unresolved Issues. (J Brian Houston, University of Manchester; Manchester, UK) In vitro kinetic studies designed to assess transporter-mediated drug-drug interactions provide a valuable qualitative assessment of inhibitory potency. However quantitative DDI predictions remain challenging due to several unresolved issues in both the conduct of in vitro studies and the models used in prediction strategies. These include: time dependent metrics for uptake process, parallel passive and active transport pathways and resolution of membrane transport from intracellular active processes.

10:45 AM – 11:15 AM

The Prediction of Complex Transporter (uptake, efflux)/Enzyme-mediated Drug-drug Interactions be Possible Using a Proposed Physiologically-based Pharmacokinetic (PBPK) Model with In Vitro Ki Values ? (Yuichi Sugiyama, Sugiyama Laboratory, RIKEN Innovation Center, RIKEN, Research Cluster for Innovation, RIKEN; Yokohama, Japan) Recent reports provided quantitative predictions for OATP-mediated DDIs between statins and cyclosporine A(CsA)/rifampicin(RIF) based on PBPK models. In the process of the analyses, the in vitro–in vivo discrepancies in the Ki values for OATPs were suggested. Such discrepancies may hamper the practical use of PBPK modeling for DDI prediction via a bottom-up approach, in which model parameters are determined by scaling up in vitro experimental results. Therefore, optimization of pharmacokinetic parameters of several drugs to account for the clinical data (providing in vivo parameters) will improve the accuracy of a global in vitro-in vivo extrapolation (IVIVE) methodology. Taking a top-down approach, the present study aimed to construct a widely applicable method for optimizing PBPK model parameters that describe adequately the clinically observed interactions between statins and CsA/RIF, which were primarily caused by the inhibition of hepatic OATPs.

11:15 AM – 11:45 AM

Mechanism-based P450 inhibition: Scientific Concepts and Relevance to Drug Development (Larry Wienkers, Amgen, Thousand Oaks, CA). Mechanism-based inactivation

(MBI) of cytochrome P450 (P450) enzymes represents several challenges for the development of therapeutics. Foremost, MBI has the potential to amplify the magnitude of a drug-drug interaction by changing the clearance of coadministered drugs and ultimately affecting patient safety. The MBI-mediated rate of inactivation relative to a zero-order synthesis rate of new enzyme provides a path for estimating the magnitude of MBI inhibition of drug disposition. However, reactive metabolites, often the precursors to MBI, are less understood, and predicting the impact of the reactive metabolites on safety is difficult. This lecture will review the current understanding of the mechanism of bioactivation of P450 inhibitors, as well as approaches to characterize the chemical entities that predispose to MBI.

11:45 AM – 12:15 PM

Physiologically Relevant In Vitro Experimental Systems for DDI Evaluation: Novel Approaches with Human Hepatocytes (Albert P. Li, *In Vitro ADMET Laboratories, Inc.; Columbia, MD*) Since our inaugural publication on successful cryopreservation of hepatocytes in 1989, cryopreserved human hepatocytes are now considered the “Gold Standard” for in vitro evaluation of human drug properties including metabolic fate, drug-drug interaction potential, and hepatotoxicity. This lecture will review the state of the art of the application of human hepatocytes in the evaluation of drug-drug interactions. Novel applications, including the “plated hepatocyte relay assay” for the evaluation of slowly metabolized chemicals (U. S. patent allowed). A new hepatocyte system, the MetMax™ Cryopreserved Hepatocytes (patent pending) as a one-step “thaw and use” system for drug metabolism and drug-drug interaction evaluations, will also be described.

12:15 PM – 2:00 PM – LUNCH BREAK

2:00 PM – 2:30 PM – SESSION 1 PANEL DISCUSSION

Session 2: Regulatory perspectives and clinical practice (Chair: Isabelle Ragueneau-Majlessi)

2:30 PM – 3:00 PM

20 years of Progress in Drug-drug Interaction Evaluation: Overview of the Literature and NDA Reviews (Isabelle Ragueneau-Majlessi, *University of Washington; Seattle, WA*) Since the publication of the first FDA guidance documents for the evaluation of pharmacokinetic drug-drug interactions, tremendous advancements have been made in the approaches to accurately assess the risk of clinically significant changes in drugs exposure. This lecture will review the notable advancements based on the Literature and NDA reviews published in the past two decades.

3:00 PM – 3:30 PM

Recommendations for Patient-Specific Drug Interaction Decision Support (Phil Hansten, *University of Washington, Seattle, WA*) Exposure to potential drug-drug interactions (DDIs) can cause preventable patient harm and requires proper management. Many electronic prescribing and medication information systems include interruptive alerts and non-interruptive information as forms of clinical decision support (CDS) to warn clinicians that potential DDIs exist based on a patient's medication history. DDI alerts most commonly occur during the prescriber medication order entry or the pharmacist dispensing/verification process. The Centers for Medicare & Medicaid Services (CMS) included DDI screening in the

agency's guidelines for achieving meaningful use of electronic health records (i.e., CMS Meaningful Use Core Measure). Today, every pharmacy and increasing numbers of physician offices and healthcare organizations in the United States employ some form of health information technology that includes DDI alerts.

3:30 PM – 4:00 PM

Application of Evidence Based, Patient Specific Drug Interaction Screening (John Horn, *University of Washington; Seattle, WA*) Computer drug interaction alerts are notorious for low sensitivity and countless irrelevant alerts leading to generalized desensitization to all drug interaction alerts, known as alert fatigue. Several methods have been employed by end users to avoid alert fatigue. Understanding the strengths and limitations of these approaches is critical to the development of advanced approaches for appropriate drug interaction screening.

4:00 PM – 4:30 PM – BREAK

4:30 PM – 5:00 PM

Comparing Various In Vitro Prediction Criteria to Assess the Potential of a New Molecular Entity to Inhibit Organic Anion Transporting Polypeptide 1B1. (Lei Zhang, *Invited; Silver Spring, MD*) Evaluation of organic anion transporting polypeptide (OATP) 1B1-mediated drug-drug interactions (DDIs) is an integral part of drug development and is recommended by regulatory agencies. In this presentation, various prediction methods and cutoff criteria based on in vitro inhibition data to assess the potential of a new molecular entity to inhibit OATP1B1 in vivo will be reviewed.

5:00 PM – 5:30 PM

Cryopreserved Human Enterocytes for the Evaluation of Drug-drug and Food-drug Interactions (Albert P. Li, *In Vitro ADMET Laboratories, Inc.; Columbia, MD*) It is now known that orally administered drugs may be extensively metabolized in the intestinal tract, with enterocytes as the major cell type responsible for xenobiotic metabolism. Drug bioavailability is therefore a function of both intestinal permeability and metabolism. Further, bioavailability may also be influenced by intestinal drug-drug and food-drug interactions. In our laboratory, cryopreserved enterocytes have been developed for the assessment of intestinal drug metabolism and drug-drug interactions. Properties of the cryopreserved enterocytes and their application in the evaluation of intestinal drug metabolism and intestinal drug/drug and food/drug interactions will be presented.

5:30 PM – 6:00 PM – SESSION 2 PANEL DISCUSSION

END OF DAY 1

TUESDAY, JUNE 20, 2017
DDI-2017 - Day 2

7:00 AM – 8:00 AM – REGISTRATION

Session 3: Extended Clearance Concept in Drug Interactions (Chair: Jashvant Unadkat)

8:00 AM – 8:30 AM

Transport vs. metabolism: What determines the PK and PD of drugs? Insights from the Extended Clearance Model? (*Jashvant Unadkat, University of Washington; Seattle, WA*) The implications of the ECM on PK/PD of drugs will be reviewed in this lecture. The well-stirred hepatic clearance model (WSHM) has been expanded to include drug transporters (i.e., extended clearance model [ECM]). However, the consequences of this expansion in understanding when transporters vs. metabolic enzymes will affect the pharmacokinetic (PK) and pharmacodynamic (PD) of drugs remains opaque. Identifying the rate-determining step(s) in systemic or tissue drug PK/PD will allow accurate predictions of drug PK/PD and drug-drug interactions (DDIs).

8:30 AM – 9:00 AM

The Application of the Extended Clearance Classification System in Projecting ADME Behavior and Drug-Drug Interactions in Early Discovery and Development: Industrial Perspective (*Ayman El-Kattan, Pfizer, Inc.; Cambridge, MA*). To assess the utility of Extended Clearance Classification System (ECCS) in understanding absorption, distribution, metabolism, and elimination (ADME) attributes and enabling victim drug-drug interaction (DDI) predictions. A database of 368 drugs with relevant ADME parameters, main metabolizing enzymes, uptake transporters, efflux transporters, and highest change in exposure (%AUC) in presence of inhibitors was developed using published literature. Drugs were characterized according to ECCS using ionization, molecular weight and estimated permeability. Results show that ECCS is useful in drug development, providing a framework to project ADME profiles and further enables prediction of victim DDI liabilities in drug discovery and development.

9:00 AM – 9:30 AM

Predicting Transporter-mediated PK and DDIs: Building a framework and gaining confidence (*Manthana Varma, Pfizer, Inc.; Cambridge, MA*). A large body of evidence suggests hepatic uptake transporters, organic anion-transporting polypeptides (OATPs), are of high clinical relevance in determining the pharmacokinetics of substrate drugs, based on which recent regulatory guidances to industry recommend appropriate assessment of investigational drugs for the potential drug interactions. We recently proposed an extended clearance classification system (ECCS) framework in which the systemic clearance of class 1B and 3B drugs is likely determined by hepatic uptake. The ECCS framework therefore predicts the possibility of drug-drug interactions (DDIs) involving OATPs and the effects of genetic variants of SLCO1B1 early in the discovery and facilitates decision making in the candidate selection and progression. Although OATP-mediated uptake is often the rate-determining process in the hepatic clearance of substrate drugs, metabolic and/or biliary components also contribute to the overall hepatic disposition and, more importantly, to liver exposure. Clinical evidence suggests that alteration in biliary efflux transport or metabolic enzymes associated with genetic polymorphism leads to change in the pharmacodynamic response of statins, for which the pharmacological target resides in the liver. Perpetrator drugs may show inhibitory and/or induction effects on transporters and enzymes simultaneously. It is therefore important to adopt models that frame these multiple processes in a mechanistic sense for quantitative DDI predictions and to deconvolute the effects of individual processes on the plasma and hepatic exposure. In vitro data-informed mechanistic static and physiologically based pharmacokinetic models are proven

useful in rationalizing and predicting transporter-mediated DDIs and the complex DDIs involving transporter-enzyme interplay.

9:30 AM – 10:00 AM – SESSION 3 PANEL DISCUSSION

10:00 AM – 10:30 AM - BREAK

Session 4

Session 4: Drug metabolites as contributors to drug interactions (Chair: Jan Wahlstrom)

10:30 AM – 11:00 AM

Drug Metabolites as Contributors to Clinical Drug-drug Interactions: AstraZeneca Perspectives (*Ken Grime, AstraZeneca R&D; Gothenburg, Sweden*) Only a very small number of drug metabolites have been implicated as primary perpetrators of clinical drug-drug interactions (DDI). Regulatory guidance states that metabolites present at greater than 10% of total drug-related exposure in humans, or 25% of the parent exposure, should trigger further investigation of their inhibitory potency. The presentation will highlight the need for vigilance in predicting likely drug-drug interactions and show that detailed analyses are required early in clinical drug development when considering possible interactions involving drug metabolites.

11:00 AM – 11:30 AM

Aldehyde Oxidase Metabolite as a Perpetrator of Drug-Drug Interactions (*Niresh Hariparsad; Vertex Pharmaceuticals, Boston, MA*) In this discussion, we highlight the role of aldehyde oxidase (AO) in the formation of a hydroxyl metabolite of Decernotinib (VX-509) which is a time dependent inhibitor (TDI) of CYP3A4. Based upon studies conducted with human liver microsomes (HLMs), VX-509 was deemed to have a low risk of causing a DDI due to inhibition of CYP3A4, however, we observed significant increases in the area under the curve (AUC) of CYP3A4 substrates which were co-administered with VX-509. Metabolite identification studies using human liver cytosol indicated that VX-509 is converted to an oxidative metabolite which is the perpetrator of the DDIs observed in the clinic. As opposed to HLM, hepatocytes contain the full complement of drug-metabolizing enzymes and transporters and can be used to assess TDI arising from non-P450-mediated metabolic pathways. This is an additional example in which a system-dependent prediction of TDI is evident emphasizing the advantage of using human hepatocytes as opposed to HLMs to assess DDI risk.

11:30 AM – 12:00 PM

clinical inhibition caused by metabolites (*Jan Wahlstrom, Amgen, Inc.; Thousand Oaks, CA*) Quantitative prediction of the magnitude of drug-drug interactions (DDI) is critical to underwriting patient safety in the clinical setting. Key mechanistic information can help to inform physiologically-based modeling and enable reasonable predictions of DDI magnitude, including complex scenarios such as inhibitory metabolites. This presentation will focus on integrating in vitro, preclinical and clinical data to develop quantitative predictions for DDIs due to metabolite-mediated inhibition or inactivation.

12:00 PM – 2:00 PM – LUNCH BREAK

CONTINUED

Session 4: Drug metabolites as contributors to drug interactions

(Chair: Jan Wahlstrom)

2:00 PM – 2:30 PM

Regulation of P450 Expression by Drug Metabolites (*Nina Isoherranen, University of Washington, Seattle, WA*) Over recent years there has been much attention to the role drug metabolites play in inhibitory drug-drug interactions. Testing for CYP inhibition by metabolites and incorporation of metabolites into DDI predictions has allowed many previously poorly predicted DDIs to be quantitatively predicted. However, several significant gaps in drug-drug interaction predictions have remained, most notably in predicting and evaluating downregulation of CYP enzymes and induction of CYP enzymes by multiple inducer systems such as drugs and their metabolites. This presentation will focus on case examples of CYP downregulation by drugs and their metabolites. Theoretical and practical in vitro to in vivo extrapolation methods on how to predict in vivo changes in CYP expression as a result of regulation by multiple compounds will also be presented.

2:30 PM – 3:00 PM – SESSION 4 PANEL DISCUSSION

Session 5: Drug-transporter Interactions
(Chair: Kenneth Brouwer)

3:00 PM – 3:30 PM

Evaluation and Quantitative Prediction of Renal Transporter-Mediated Drug-Drug Interactions (*Bo Feng, Pfizer Inc.; Groton, CT*) With numerous drugs cleared renally, inhibition of uptake transporters localized on the basolateral membrane of renal proximal tubule cells, eg, organic anion transporters (OATs) and organic cation transporters (OCTs), may lead to clinically meaningful drug-drug interactions (DDIs). Additionally, clinical evidence for the possible involvement of efflux transporters, such as P-glycoprotein (P-gp) and multidrug and toxin extrusion protein 1/2-K (MATE1/2-K), in the renal DDIs is emerging. Herein, we review recent progress regarding mechanistic understanding of transporter-mediated renal DDIs as well as the quantitative predictability of renal DDIs using static and physiologically based pharmacokinetic (PBPK) models. Generally, clinical DDI data suggest that the magnitude of plasma exposure changes attributable to renal DDIs is less than 2-fold, unlike the DDIs associated with inhibition of cytochrome P-450s and/or hepatic uptake transporters. It is concluded that although there is a need for risk assessment early in drug development, current available data imply that safety concerns related to the renal DDIs are generally low. Nevertheless, consideration must be given to the therapeutic index of the victim drug and potential risk in a specific patient population (eg, renal impairment). Finally, in vitro transporter data and clinical pharmacokinetic parameters obtained from the first-in-human studies have proven useful in support of quantitative prediction of DDIs associated with inhibition of renal secretory transporters, OATs or OCTs.

3:30 PM – 4:00 PM

Inhibition of Human Hepatic Bile Acid Transporters as Contributing Factors to Drug-Induced Liver Injury (*Jonathan P. Jackson, Kimberly M. Freeman, Chris Black, Robert L. St. Claire III, and Kenneth R. Brouwer. Qualyst Transporter Solutions; Durham, NC*) Cholestatic drug-induced liver injury (DILI) potential in humans has been associated with bile salt export pump (BSEP) inhibition; however, in vitro BSEP

inhibition potency determinations have not been demonstrated to strongly correlate with in vivo cholestatic DILI severity. In vivo concentrations of bile acids (BA) are tightly regulated through synthesis, metabolism and transport. However, impaired BA efflux alone is not an adequate predictor of DILI. Under cholestatic conditions, an adaptive response regulated by FXR initiates a basolateral bile acid efflux mechanism via OST α/β to reduce the intracellular concentration of bile acids in the hepatocyte. Chenodeoxycholic acid (CDCA) was used as a model BA to demonstrate FXR activation (decreased CYP7A1 expression, induction of OST α/β and BSEP measured by gene expression) following chronic exposure in Transporter Certified™ sandwich-cultured human hepatocytes (SCHH). The gene expression changes were linked to functional changes in the total bile acid pool and B-CLEAR® technology was used to evaluate the hepatobiliary disposition of endogenous bile acids. Our results suggest that to properly assess a drug candidate's cholestatic DILI potential, an assay platform should include a fully integrated cell system (e.g., SCHH) capable of generating this adaptive response, and integrating the acute and chronic effects of the drug candidate on the hepatobiliary disposition of bile acids.

4:00 PM – 4:30 PM – BREAK

4:30 PM – 5:00 PM

Drug Metabolism and Transport at the Therapeutic Site of Action (*Robert S. Foti, Amgen Inc.; Cambridge, MA*) In addition to hepatic and intestinal metabolism, the efficacy, safety and metabolism of small molecules and protein therapeutics can be impacted by enzyme and transporter activity at the therapeutic site of action. Metabolism in tissues such as brain and lung, active transport of small molecules at the site of action and transcytosis or catabolism of protein therapeutics across physiological barriers or within cells can all affect the pharmacological, metabolic and drug interaction profiles of a potential therapeutic agent. This talk will aim to highlight some of the recent findings and future directions surrounding this emerging area of research.

5:00 PM – 5:30 PM

Application of endogenous probes for early assessing drug-drug interactions in human (*Yurong Lai, Bristol-Myers Squibb Company; Princeton, NJ*) In the present study, an open-label, three-treatment, three-period clinical study of rosuvastatin (RSV) and rifampicin (RIF) when administered alone and in combination was conducted in 12 male healthy subjects to determine if coproporphyrin I (CP-I) and coproporphyrin III (CP-III) could serve as clinical biomarkers for organic anion transporting polypeptide 1B1 (OATP1B1) and 1B3 that belong to the solute carrier organic anion gene subfamily. Genotyping of the human OATP1B1 gene was performed in all 12 subjects and confirmed absence of OATP1B1*5 and OATP1B1*15 mutations. Average plasma concentrations of CP-I and CP-III prior to drug administration were 0.91 $\pm$ 0.21 and 0.15 $\pm$ 0.04 nM, respectively, with minimum fluctuation over the three periods. CP-I was passively eliminated, whereas CP-III was actively secreted from urine. Administration of RSV caused no significant changes in the plasma and urinary profiles of CP-I and CP-III. RIF markedly increased the maximum plasma concentration (C_{max}) of CP-I and CP-III by 5.7- and 5.4-fold (RIF) or 5.7- and 6.5-fold (RIF+RSV), respectively, as compared with the predose values. The area under the plasma concentration curves from time 0 to 24 h (AUC_{0–24h}) of CP-I and CP-III with RIF and RSV increased by 4.0- and 3.3-fold,

respectively, when compared with RSV alone. In agreement with this finding, C_{max} and AUC_{0–24h} of RSV increased by 13.2- and 5.0-fold, respectively, when RIF was coadministered. Collectively, we conclude that CP-I and CP-III in plasma and urine can be appropriate endogenous biomarkers specifically and reliably reflecting OATP inhibition, and thus the measurement of these molecules can serve as a useful tool to assess OATP drug-drug interaction liabilities in early clinical studies.

5:30 PM – 6:00 PM – SESSION 5 PANEL DISCUSSION

END OF DAY 2

WEDNESDAY, JUNE 21, 2017
DDI-2017 - Day 3

7:00 AM – 8:00 AM – REGISTRATION

Session 6: Enzyme Induction and nuclear receptors
(Chair: Jane Kenny)

8:00 AM – 8:30 AM

Using Rifampicin Data and Models to Guide Assessment of Clinically Significant CYP3A4 Induction Risk (*Jane R. Kenny, Genentech; S. San Francisco, CA*) Quantitatively accurate prediction of clinical CYP3A4 induction potential remains challenging. Here an approach to enhance the accuracy of prediction using physiologically-based pharmacokinetic modeling calibrated to clinical rifampicin response will be discussed alongside important considerations of in vitro data for model input.

8:30 AM – 9:00 AM

Acute and persistent gene expression effects upon neonatal exposure to PXR and CAR ligands (*Julia Yue Cui, University of Washington; Seattle, WA*) Safety concerns have emerged regarding the potential long-lasting effects due to developmental exposure to xenobiotics. The pregnane X receptor (PXR) and constitutive androstane receptor (CAR) are critical xenobiotic-sensing nuclear receptors that are highly expressed in liver. Results will be represented on a study to test the hypothesis that neonatal exposure to PXR- or CAR-activators not only acutely but also persistently regulates the expression of drug-processing genes (DPGs). Neonatal exposure to both PCN and TCPOBOP persistently down-regulated multiple Cyp4a members, which are prototypical-target genes of the lipid-sensor PPAR α , and this correlated with decreased PPAR α -binding to the Cyp4a gene loci. RT-qPCR, western blotting, and enzyme activity assays in livers of wild-type, PXR-null, and CAR-null mice confirmed that the persistent down-regulation of Cyp4a was PXR and CAR dependent. In conclusion, neonatal exposure to PXR- and CAR-activators both acutely and persistently regulates critical genes involved in xenobiotic and lipid metabolism in liver.

9:00 AM – 9:30 AM – SESSION 6 PANEL DISCUSSION

Session 7: Novel approaches in drug interactions
(Chair: Theunis Goosen)

9:30 AM – 10:00 AM

Novel Cytochrome P450 Reaction Phenotyping for Low-Clearance Compounds Using the Hepatocyte Relay Method (*Li Di Pfizer, Inc.; Cambridge, MA*) Determination of fraction metabolized by drug-metabolizing enzymes (i.e., reaction phenotyping) is critical for drug candidates to: 1) understand the potential risk associated with being a victim of drug-drug interaction; 2) estimate the impact of genetic polymorphic enzymes on in vivo exposure; and 3) anticipate inter-subject pharmacokinetic variability for compounds with a narrow therapeutic index. A novel cytochrome P450 reaction phenotyping method for low-clearance compounds has been developed for eight P450 enzymes (CYP1A2, 2B6, 2D6, 2C8, 2C9, 2C19, 3A, and 3A4) and pan-P450 using the hepatocyte relay approach. Selective mechanism-based inhibitors were used to inactivate the individual P450 enzymes during preincubation, and inactivators were removed from the incubation before adding substrates to minimize reversible inhibition and maximize inhibitor specificity. The inhibitors were successfully applied to the hepatocyte relay method for P450 reaction phenotyping of low-clearance compounds. This novel method provides a new approach for determining the fraction metabolized of low-turnover compounds that are otherwise challenging with the traditional methods, such as chemical inhibitors with human liver microsomes and hepatocytes or human recombinant P450 enzymes.

10:00 AM – 10:30 AM – BREAK

10:30 AM – 11:00 AM

Characterization of UGT Inhibition as a Necessary and Important Strategy in Drug Development (*Theunis C. Goosen, Pfizer Inc.; Groton, CT*) Assessment of human UDP-glucuronosyltransferase (UGT) drug-drug interaction (DDI) liability, both as perpetrator and victim, is highlighted in regulatory agency DDI guidance for pharmaceutical industry. This emerging guidance reflects the scientific advances in in vitro assays developed to characterize UGT inhibition. Nevertheless, there are potential limitations in our ability to assess the contribution of UGTs to overall metabolic drug clearance and eventual clinical DDI interaction risk. Since an increasing number of new chemical entities are primarily cleared through UGT-mediated metabolism, establishing the clinical relevance of UGT-mediated DDI is becoming significant through all phases of drug development. Reagents and protocols need to be established and a validation set of compounds with clearance or DDI perpetration analyzed for in vitro-in vivo extrapolation (IVIVE). In addition, the utility of modeling and simulation approaches, including physiologically-based pharmacokinetic (PBPK) models are increasingly evident in the prediction of the DDI risk profile of drugs cleared by UGTs. Application of PBPK modeling concepts will be illustrated using drug development examples to demonstrate the diversity in scientific and regulatory points of view in modeling and simulation to address UGT-mediated DDI in new drug development.

11:00 AM – 11:30 AM

Physiologically Based Pharmacokinetic Model of Organic Anion Transporting Polypeptide Victim Drug using Human Hepatocytes Cultured in Human Plasma Data (*Jialin Mao, Genentech; S. San Francisco, CA*) It is known that a scaling factor is typically required when the in vitro uptake data are utilized to predict the pharmacokinetic profile of OATP substrates. Culturing of hepatocytes in human plasma is a novel system which may allow the direct in vitro and in vivo

extrapolation. A PBPK model of pravastatin using the OATP kinetic data generated in plateable human hepatocytes cultured in human plasma was developed to simulate the intravenous and oral plasma concentration-time profiles successfully without incorporating a scaling factor.

11:30 AM – 12:00 PM

Physiologically Based Pharmacokinetic Model for Itraconazole Pharmacokinetics and Drug–Drug Interaction Prediction (*Yuan Chen; Genentech; S. San Francisco, CA*) Physiologically based pharmacokinetic (PBPK) modeling for itraconazole has been challenging due to highly variable in vitro data used for ‘bottom-up’ model building. Under-prediction of pharmacokinetics and drug–drug interactions (DDIs) following multiple doses of itraconazole has limited the use of PBPK model simulation to aid an itraconazole clinical DDI study design. This lecture will describe a novel approach: an itraconazole PBPK model built using a mixed ‘top-down’ and ‘bottom-up’ approach to enable a more accurate pharmacokinetic and DDI prediction, allowing PBPK model simulations to optimize clinical itraconazole DDI study design.

12:00 PM – 12:30 PM – SESSION 7 PANEL DISCUSSION

12:30 PM – 2:30 PM – LUNCH BREAK

**Session 8: Biologics-Drug Interactions
(Chair: Stephen Wang)**

2:30 PM – 3:00 PM

DDI Potential Assessment and Challenges for Therapeutic Proteins and ADCs (*Elimika Pfuma Fletcher, U.S. Food and Drug Administration; White Oak MD*) DDI assessments are more established for small molecules. The effect of small molecules on therapeutic proteins through metabolism or transporters is limited, but some therapeutic proteins can have DDI effects through modulation of cytokines. Payloads in ADC have the same DDI risks as small molecules, but challenges arise in mitigation strategies such as dose adjustment for the ADC. This talk will focus on the assessment of DDI potential of therapeutic proteins and ADCs and the challenges in the management of DDIs.

3:00 PM – 3:30 PM

Human Pharmacokinetics and Pharmacodynamics Predictions for mAbs Exhibiting Target-mediated Drug Disposition: Case Study Examples (*Pratap Singh, Alexion Pharmaceuticals; New Haven, CT*) A significant portion of the monoclonal antibodies (mAbs) currently on the market or in clinical trials exhibit target mediated drug disposition (TMDD) due to the clearance of the drug-target complex upon binding. mAbs with TMDD exhibit non-linear pharmacokinetics, a process that is saturable at a sufficiently high dose. In this talk, basic principle driving the mAb TMDD phenomena and key pharmacokinetic/pharmacodynamic (PK/PD) considerations will be highlighted using case study examples. In particular, translation from preclinical to clinic, as well as human dose and target coverage predictions will be illustrated using mechanistic modeling approaches. Further, current gaps and challenges associated with fully characterizing the TMDD phenomena will be presented along with ongoing research to develop a quantitative approach towards robust predictions of mAb TMDD in clinical settings.

3:30 PM – 4:00 PM

DDI of Biologics, Pfizer Experience (*Stephen Wang, Pfizer, Inc.; Cambridge, MA*) Biologics represent a major effort in drug development in the pharmaceutical industry. In this lecture, the collective experience in Pfizer on the drug-drug interaction potential of biologics will be reviewed. Challenges in this field and recommendations for future studies will be presented.

4:00 PM – 4:30 PM

Transporters and Antibody Drug Conjugates: A Fresh Perspective (*Nagendra Chemuturi, Seattle Genetics, Bothell, WA*) Antibody Drug Conjugates (ADCs) have emerged as a new modality in the treatment of cancer. They combine the specificity of an antibody, for receptors on tumor cells, to selectively deliver potent cytotoxins to tumor cells rather than healthy cells. Around 30 ADCs are being investigated in various cancer indications. The in vivo disposition of an ADC is an interplay between its three components including the small molecule cytotoxin, which can be a transporter substrate. The purpose of the current talk is to provide an insight into current knowledge of ADME properties of ADCs with focus on how transporters affect various aspects of ADCs.

4:30 PM – 5:30 PM – SESSION 8 PANEL DISCUSSION

5:30 PM – 6:00 PM

Concluding Remarks (Albert P. Li)

END OF DAY 3

END OF CONFERENCE

About Institute for Scientific Communications, Inc.

The Institute for Scientific Communication is a not-for-profit organization with the mission to distribute scientific knowledge via effective communications. ISC sponsors conferences and workshops to allow exchange of scientific observations and ideas, with the ultimate goal being timely application of the latest scientific discoveries to better human lives. Please visit our web site at www.ifscomm.org.

POSTER PRESENTATIONS:

Poster Presentations are always encouraged. Please submit your poster abstract for approval by the organizing board by May 20th. Poster size should be no larger than **3 feet high by 6 feet long**. Abstracts of posters will be included in the conference materials and will be available on the ISC website. The conference materials will be posted on the basis of availability from the author or presenter. There is no formal poster presentation scheduled. All posters will remain displayed throughout the conference. Please be prepared to display your poster during registration on Sunday, June 19th or before the first session begins on Monday, June 20th. Poster presenters will have ample time for discussion during breaks and Panel discussions. Submit posters abstracts for approval to Nola Mahaney, ISC; 9221 Rumsey Road, Suite # 8; Columbia, MD 21045 or email files attachment to nola@ifscomm.org. Approved poster applicants are responsible for completing a conference attendance registration form and payment of fee - visit www.ifscomm.org - and for the shipping of the poster itself. Please contact Nola Mahaney for any questions or comments. Please refer to "Travel Information" for hotel address and shipping information.

The conference will be held at
Husky Union Building, University of Washington;
4001 NE Stevens Way, Seattle, WA 98195
(206) 543-8131

TRAVEL INFORMATION:

The Watertown is conveniently located just four blocks from the University of Washington. There's no better home base if you're checking out campus, visiting a nearby medical facility, hosting a business event or simply want to see everything that makes Seattle a world-class city. Here you'll enjoy the kind of service that only a boutique hotel can offer including 102 smoke-free rooms, complimentary breakfast bar and a warm, inviting staff at your service 24 hours a day.

Amenities: Complimentary Shuttle Service; Bicycle Checkout Program; Dog Friendly Seattle Hotel; Earth-Friendly Seattle Hotel. Please click on watertownseattle.com more details.



WATERTOWN

A UNIQUE URBAN HOTEL

**4242 Roosevelt Way NE
Seattle, WA 98105
telephone: (425) 974-7133
fax: (206) 547-4937**

Guest Room Rates: Studio Double Queen Suite (SDQS) and Board Room Suite (BRS) \$185.00 +tax, single/double occupancy. Add \$20.00 per each additional adult per room.

- Check in begins at 4:00 • Check out time is 12:00 noon.
- Rates are subject to all applicable taxes and assessments, currently 15.6%
- Group rate will be available three (3) nights pre/ post event based upon the availability of this rate at the time of request.
- Rate includes Complimentary Wireless Internet Access and local phone calls.

METHOD OF RESERVATION: Individual call-in. Guests must e-mail reservations@staypineapple.com or call 866.866.7977 before Thursday, May 18, 2017 to secure their guest rooms. Guests should reference "Institute for Scientific Communications" to receive the group rate.

The online booking code is **170617DDI2**. In order for your guests to book online they just need to follow the directions below. Please note that the online booking code will only work for contracted room nights. If a guest would like to come in early or stay a day later then they will need to make their reservation by calling our reservations department at 866-866-7977 or emailing them at reservations@staypineapple.com

- go to either watertownseattle.com
- click reservations
- put in check in and check out date
- click book now
- click optional fields tab
- put 170617DDI2 in group code section
- click modify

Hotel guests have access to each property's amenities. Watertown guests may use the pool at University Inn and University Inn guests may use the fitness room and free road bikes offered at Watertown. Both hotels offer complimentary guest laundry facilities.

Conference Registration Payment

Payment may be made by check or credit card. Checks should be made in US \$, payable to Institute for Scientific Communications, Inc. Mail to: **ISC, Inc., 9221 Rumsey Road, Suite # 8, Columbia, MD 21045, USA**

Cancellation Policy

All cancellations are subjected to a \$250.00 cancellation fee. Longer than 30 days, 100% refund (less cancellation fee). Less than 30 days, no refund but registration may be transferred to another person. All refund requests must be in writing. All refunds will be issued after the meeting has occurred. No refunds requests will be accepted after May 29, 2015. Please submit cancellation and refund requests including transferring of registration to: Fax: 410-869-9560; E-mail: nola@ifscomm.org; **Cancel Deadline: May 19, 2017**

Registration Form AVAILABLE ONLINE AT
WWW.IFSCOMM.ORG Email to nola@ifscmm.org with
remittance to: ISC, Inc. 9221 Rumsey Road, Suite # 8;
Columbia, MD 21045, USA; FAX No: (410) 869-9560.
Payment may be made by check in US\$, payable to **Institute
for Scientific Communications, Inc.** or by credit card.

Academic/Government participants will receive a 50% discount.

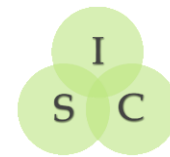
Contact Nola Mahaney for Exhibitor or Sponsorship Opportunities at nola@ifscmm.org or phone (410) 869-9166; or visit <http://www.ifscmm.org>.

DDI-2017 is sponsored in part by:

FEATURED EXHIBITORS



University of Washington
Metabolism and Transport
Drug Interaction Database

REGISTRATION FORM: DDI-2017Or please register online at: <http://www.ifscomm.org/>Institute
for
Scientific
Communication**A. Credit Card Information:*****Required fields to be completed*****American Express** _____ **VISA** _____ **MC** _____***Cardholder Name:**

***Cardholder Billing Address:**

***Cardholder Billing City:**

***Cardholder Billing State / Zip (Postal) Code:**

***Cardholder Phone #:**

***Cardholder Email:**

***Card Number:**

***Expiration Date:**

***3 or 4 Digit Security Code:**

Amount: U.S. \$*DDI-2017 Registration Fee Schedule**

Event Name	Registration Fee	Registration Fee	Exhibitor Fee
	Until May 19, 2017	After May 19, 2017	
DDI-2017	\$ 1,250.00	\$ 1,500.00	\$ 2,000.00

B. Registrant Information:

Dr. _____ Mr. _____ Ms. _____

Please type your name as you wish it to appear on your name badge

PLEASE PRINT

Last Name First Name Mid. Initial

Job Title

Company/Agency/Institution

Address 1

Address 2

City State Postal Code

Country

Telephone FAX

Email Address

How did you hear about this meeting?

Colleague _____ Web Site _____

Brochure _____ Calendar Listing _____

E-mail _____ Journal Ad _____

ALL PRICES ARE SHOWN IN US CURRENCY