DDI-2019

22nd International Conference on Drug-Drug Interactions:
Regulatory Issues; Literature and NDA Review; Enzyme and Transporter Induction; In Vivo Preclinical and Clinical Approaches; Complicating Factors in DDI Evaluation; Hepatic versus Extrahepatic DDI; Drug Induced Liver Injuries

June 20-22, 2019

Kane Hall Room 110, University of Washington; Seattle, WA 98195 USA

REGISTRATION DISCOUNT UNTIL MAY 20, 2019

DDI-2019 MEDIA PARTNER

Featuring the Following Experts: Albert P. Li; Ken Thummel; Jingjing Yu; Savannah McFeely; Sophie Argon; Chandra Prakash; Theunis Goosen; Lei Zhang; Mary Paine; Justin Lutz; Nagai Mika; Manthena Varma; Xiaoyan Chu; Erin Schuetz; Jashvant D. Unadkat; Bosse Lindmark; Nina Isoherranen; Jialin Mao; Leslie Benet; Bhagwat Prasad; Kenneth Brouwer; Kim Brouwer; Yan Zhang; Congrong Niu; Diane Ramsden; Kan He

DDI-2019 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.

PLEASE VISIT US ONLINE AT WWW.IFSCOMM.ORG
22nd International Conference on Drug-Drug Interactions

THURSDAY, JUNE 20, 2019

DDI-2019 – 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: DDI Hot Topics (Ken Thummel, University of Washington; Seattle, WA)

Session 1: 2018 DDI Review
(Chair: Jingjing Yu)

8:50 AM – 9:20 AM
OATP1B Inhibition: A comprehensive Review of the Clinical and Preclinical Interaction Data (Savannah McFeely, University of Washington; Seattle, WA) In recent years, the impact of the OATP1B transporters on drug-drug interactions (DDIs) has become a focus of research, and the evaluation of their role in drug disposition is recommended by regulatory agencies worldwide. While inhibitors of OATP1B1/1B3 have been identified in the literature and probe drugs have been proposed by some regulatory agencies, there is no general consensus on the ideal compounds to be used for clinical DDI studies. The aim of our work was twofold: to provide a thorough analysis of the available in vitro and in vivo data regarding OATP1B1/1B3 inhibitors and, from the identified compounds, propose the most selective as potential clinical tools.

9:20 AM – 9:50 AM
Review of the 2018-2019 Literature on Drug Interactions (Sophie Argon, University of Washington; Seattle, WA) "Critical Review of the literature": The presentation will provide an overview of the most recent drug-drug interactions publications (2018-early 2019) and will analyze enzyme- and transporter-based DDIs. The most pronounced clinical interactions will be highlighted and a few clinical studies will be presented in more details to illustrate the mechanisms involved and discuss the clinical relevance of the results.

9:50 AM – 10:20 AM – BREAK

10:20 AM – 10:55 AM
Mechanistic Analysis of Pharmacokinetic DDIs and Clinical Relevance with Drugs Approved by the FDA in 2018 (Jingjing Yu, University of Washington, Seattle, WA) Drug-drug interaction data obtained from New Drug Application reviews with drugs approved by the US Food and Drug Administration in 2018 were systematically analyzed using a mechanistic and quantitative approach. Key findings including metabolism- and transporter-mediated in vitro and clinical studies were reviewed, and drug interactions with possible significant clinical relevance were identified.

10:55 AM – 11:25 AM - SESSION 1 PANEL DISCUSSION

11:25 AM – 1:30 PM – LUNCH

Session 2: Regulatory Issues
(Chair: Lei Zhang)

1:35 PM – 2:05 PM
Physiologically Based Pharmacokinetic Model Predictions of Ivosidenib as a Victim and Perpetrator of Drug-Drug Interactions: An industrial perspective (Chandra Prakash, Agios Pharmaceuticals, Inc.; Cambridge, MA) Recent regulatory guidelines describe the use of PBPK modelling and simulation at different stages of drug development, supporting the view that a well-qualified PBPK model can be used to estimate the risk of concomitant medications in clinical trial even prior to in vivo DDI studies. PBPK modeling integrates the data from various sources to not only estimate PK parameters but also to gain mechanistic insight into compound properties. This presentation will describe the development of a PBPK model for a recently approved drug, ivosidenib, using in vitro and clinical PK data from HV and its application to quantitatively predict the magnitude of drug-drug interactions (DDI) in the clinic.

2:05 PM – 2:35 PM
Lorlatinib and the Use of Induction Slope vs Measured Emax and EC50 in PBPK Modeling (Theunis Goosen, Pfizer Inc.; Groton, CT) Lorlatinib is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC). In vitro studies indicated that lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A and that it activates PXR, with the net effect in vivo being induction. The in vitro dose-dependent increase in CYP3A4 mRNA observed in cultured human hepatocytes was not saturable and typical induction parameters (Emax and EC50) could not be estimated. Clinically, lorlatinib oral clearance increased at steady-state compared to single dose, indicating autoinduction. A PBPK model was developed utilizing the initial mRNA induction slope observed in human hepatocytes and was able to recover the single- and multiple dose plasma pharmacokinetic profile of lorlatinib. Extrapolation of the verified PBPK model evaluated the DDI impact when lorlatinib is co-administered with CYP3A inhibitors as well as changes in fractional CYP3A4 clearance in the context of
complex drug-drug interactions. This study details the ability to use the induction slope in regulatory submissions for clinical inducers.

3:05 PM – 3:35 PM
Drugs-Drug Interactions and Generic Drugs (Lei Zhang, US FDA; Silver Spring, MD) In 2017, nine out of every 10 prescription drugs in the U.S. were generic drugs. Generic drugs result in significant patient savings, representing approximately 23% of prescription spending. A generic drug is the same as an already marketed brand-name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. For oral drugs that are intended for systemic actions, in addition to pharmaceutical equivalence demonstration, bioequivalence (BE) studies are critical to infer therapeutic equivalence. Although many intrinsic and extrinsic factors can affect drug exposure and their response, they usually affect the brand-name and generic drugs in the same extent. Generally, BE studies in healthy subjects tell us that products can be substituted in patients because the BE study results allow us to conclude that the formulations of brand-name and generic drugs perform the same. In this presentation, one extrinsic factor (i.e., drug interactions), will be discussed to determine putatively under what circumstances, a co-administered drug may affect a brand-name drug and generic drug differently that may warrant further research in the area.

3:35 PM – 4:05 PM – BREAK
Exhibitor Presentation

4:05 PM – 4:35 PM
Clinical Natural Product-Drug Interactions: Harvesting Precipitants and Mechanisms (Mary Paine, Washington State University; Spokane, WA) Sales of botanical and other natural products (NPs) continue to rise, increasing the risk for adverse interactions with conventional drugs. However, unlike for drug-drug interactions, rigorous guidelines for assessing potential clinically relevant NP-drug interactions are lacking. The National Center for Complementary and Integrative Health established the Center of Excellence for Natural Product-Drug Interaction Research in September 2015. A key deliverable of the Center is a set of recommended approaches to guide researchers in the proper conduct of NP-drug interaction studies. These approaches should lead to improved design of future NP-drug interaction research and ultimately, improved decisions regarding the optimal management of these complex interactions.

4:35 PM – 5:05 PM – SESSION 2 PANEL DISCUSSION

END OF DAY 1

FRIDAY, JUNE 21, 2019
DDI-2019 - Day 2

7:00 AM – 8:00 AM – REGISTRATION

8:05 AM – 8:35 AM
Drug Transporter Induction: Can We Leverage P450 Data to Streamline Our Clinical Pharmacology Programs? (Justin Lutz, Gilead Sciences, Inc.; Foster City, CA) Drug transporter and cytochrome P450 expression is regulated by shared nuclear receptors and, hence, an inducer should induce both, although the magnitude may differ. An in vivo DDI study was conducted to 1) establish relative induction relationships between CYP3A and drug transporters (P-gp, OATP and BCRP) or other P450s (CYP2C9 and CYP1A2) using ascending doses of rifampin, and 2) to determine if these relationships could be utilized to predict transporter induction by other CYP3A inducers (rifabutin and carbamazepine). Rifampin dose-dependent induction of P-gp, OATP, and CYP2C9 was always one drug–drug interaction category lower than observed for CYP3A. Furthermore, induction of P-gp and CYP2C9 by rifabutin and carbamazepine were successfully predicted by observed CYP3A induction. These results demonstrate that the effect of a PXR agonist on CYP3A can be leveraged to inform on induction liability for other primarily PXR-regulated P450s/transporters, allowing for prioritization of targeted DDI assessments during new drug development.

8:35 AM – 9:05 AM
Characterization of CYP2C Induction in Cryopreserved Human Hepatocytes and Its Application in the Prediction of the Clinical Consequences of the Induction (Mika Nagai, Kaken Pharmaceutical Co., LTD.; Kyoto, Japan) It is important to estimate and reduce the drug-drug interaction (DDI) risk in the lead optimization stage of drug discovery. In this presentation, the new in silico methods for the prediction of CYP3A4, CYP2B6, CYP2C2 induction, recently established by us, and their application to drug development and the prediction of the clinical consequences of the CYP2C9 induction will be introduced.

9:05 AM – 9:35 AM
OATP Transporters are not induced by PXR Activator Rifampin: In Vitro and In Vivo Investigation (Congrong Niu, Gilead Sciences, Inc.; Foster City, CA) Membrane transporters play a pivotal role in drug absorption, disposition, metabolism and elimination. While it is well-documented that both CYP3A and efflux transporter P-gp expressions are regulated through the activation of PXR and other nuclear receptors, controversial results exist in literatures for SLC uptake transporters such as OATP. The presentation will provide the overview of transporter gene regulations and update the audience in vitro and in vivo gene regulation data for clinically relevant uptake transporters.

9:35 AM – 10:05 AM
Observations and Recommendations Related to In Vitro and Clinical CYP3A Induction Variability and Risk Assessment from the IQ Induction Working Group (Diane Ramsden, Alnylam Pharmaceuticals; Cambridge, MA) A large set of in vitro and clinical CYP3A induction data was collected for understanding drug-drug interaction interpretation and risk assessment as they relate to the current guidelines from Regulatory agencies. This presentation will take the audience
through the data that lead to key recommendations with respect to donor number, criteria for characterizing positive and negative in vitro induction including the 2-fold cut-off, the value of negative controls, and finally indexing response to prototypical inducers.

10:05 AM – 10:35 AM – BREAK

Exhibitor Presentation

ABSORPTION SYSTEMS®

10:35 AM – 11:05 AM – SESSION 3 PANEL DISCUSSION

Session 4: In Vivo Preclinical and Clinical Approaches
(Chair: Manthena Varma)

11:05 AM – 11:35 AM
Utility of Cynomolgus Monkey in characterizing transporter-mediated disposition and DDls. (Manthena Varma, Pfizer; Groton, CT) Various in vivo animal models have been explored to assess the clinical impact of member transporters on the ADME/PK/DDls of drug candidates. However, poor protein homology between transporters in commonly used preclinical species (e.g., mice, rats and dogs) and humans often result in differences in substrate specificity, which can complicate the extrapolation of preclinical data to the clinical setting. However, transporters in the cynomolgus monkey generally exhibit high degree of homology with human isoforms, and therefore could be a useful model for ADME/PK/DDI characterization. Recent studies from our group and others focused on evaluating/understanding: (i) the IVIVE of OATPs mediated hepatic uptake in monkey, (ii) single-species scaling to predict clearance of OATP substrate drugs, (iii) IVIVE of OATP mediated DDls, (iv) utility of cocktail of Pgp/BCRP/OAT3/OATPs substrates to simultaneously assess transporter mediated DDls, and (v) transporter biomarkers. This presentation will discuss our experience on the utility of Cynomolgus monkey in characterizing transporter-mediated disposition and DDls.

11:35 AM – 12:05 PM
Clinically Relevant Probe Drugs for Transporter DDI Evaluation: Perspectives from the International Transporter Consortium (ITC) (Xiaoyan Chu, Merck; Kenilworth, NJ) Drug transporters play a critical role in the absorption and elimination of a wide range of drugs and xenobiotics. Inhibition of these transporters may cause clinically significant drug-drug interactions (DDIs). To evaluate a new molecular entity as a potential perpetrator of transporters, use of well characterized and/or clinically relevant probe substrates with good selectivity and sensitivity are critical for robust clinical DDI assessment that could inform DDI management strategy in the product labeling. This presentation will provide an overview of clinical probe drugs of key drug transporters as recommended in the recent ITC whitepaper, discuss their utility, limitations, and future direction of integrating probe drug cocktails, transporter endogenous biomarkers and mechanistic modeling to evaluate transporter-mediated DDls.

12:05 PM – 2:00 PM – LUNCH BREAK

Exhibitor Presentation

2:05 PM – 2:35 PM
Pheophorbide A: Fluorescent Bcrp Substrate to Measure Oral Drug-Drug Interactions in Real-Time In Vivo (Erin Schuetz, St Jude Children's Research Hospital; Memphis, TN) We determined that Pheophorbide A is a specific, inexpensive, fluorescent near infrared substrate probe that can be used to monitor Bcrp activity and the DDI potential of intestinal Bcrp inhibitors in real time in vivo utilizing a live animal fluorescence imaging technique. Concurrent in vitro high throughput PhA serum fluorescence measurements by simple spectrometry following oral co-administration of PhA and inhibitors is a complementary inexpensive tool to identify their BCRP DDI potential.

2:35 PM – 3:05 PM
Proteomics-informed Predictions of Tissue Concentrations of Drugs and Subsequent Verification through PET Imaging (Jashvant D. Unadkat, University of Washington; Seattle, WA) Tissue concentrations determine efficacy and toxicity of a drug. Transporter expression at the tissue: blood barrier (e.g. liver: blood or brain: blood barrier) can result in “asymmetry” or disconnect in tissue: blood concentration. In humans, except for Positron Emission Tomography (PET) or other imaging methods, it is impossible to measure tissue drug concentrations. For this reason, methods to predict such concentrations and to verify the predictions are needed. Therefore, when transporters are present at the tissue: blood barrier, we have developed a proteomics based approach to predict tissue drug concentrations through PBPK modeling and simulation. In addition, we have developed PET imaging methods to measure tissue drug concentrations in humans. These measurements will be used in the future to verify our proteomics based predictions of tissue drug concentrations. Supported by UWRAPT through funding from Biogen, Bristol-Myers Squibb, Gilead, Merck & Co., Genentech, Pfizer and Takeda.

3:05 PM – 3:35 PM – SESSION 4 PANEL DISCUSSION

3:35 PM – 4:05 PM – BREAK

Exhibitor Presentation

Session 5: In vitro-in vivo Extrapolation
(Chair: Jialin Mao)

4:05 PM – 4:35 PM
Accurate Estimation of Drug Exposure Variability due to Drug-drug Interactions Using fm,cyp Derived from Human Hepatocytes (Bo Lindmark, AstraZeneca; Gothenburg, Sweden) In this work we demonstrate that human hepatocytes
in combination with potent and selective P450 inhibitors is the preferred in vitro system for accurate prediction of fmP450. For mixed CYP3A/2D6 substrates the AUC-ratio in presence and absence of a strong CYP3A inhibitor and between poor and extensive CYP2D6 metabolizers can be predicted within 2-fold accuracy. By using hrP450 the CYP3A victim DDI-risk is substantially overpredicted.

4:35 PM – 5:05 PM
Impact of Intracellular Binding Proteins on Oxidative Metabolism and Clearance Predictions (Nina Isoherranan, University of Washington; Seattle, WA) The free drug hypothesis states that only drug molecules that are not bound to proteins such as albumin are available for receptor binding and metabolism. Based on this hypothesis metabolic intrinsic clearance and inhibition of drug metabolizing enzymes and drug transporters is typically predicted using the free, unbound drug concentrations. This talk will cover the emerging evidence that drug binding to intracellular binding proteins does in some cases facilitate metabolism and alter the role of individual metabolic enzymes in drug clearance.

5:05 PM – 5:35 PM
Towards Prospective Pharmacokinetic Prediction of OATP Substrates (Jialin Mao, Genentech; South 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 of OATP substrates. It demonstrates a hurdle for the prospective prediction of the new chemical entity as an OATP substrate. Investigation of the plated human hepatocytes and human embryonic kidney (HEK) 293 cells transfected with OATP1B1 and OATP1B3 in the presence and absence of 100% human plasma were explored, and the physiologically based pharmacokinetic modelling approach provided an opportunity to understand the in vitro and in vivo extrapolation.

5:35 PM – 6:05 PM
Protein Binding, Drug Transport and Drug Metabolism (Leslie Z. Benet, University of California San Francisco; San Francisco, CA) Accurately predicting hepatic clearance is an integral part of the drug development process, and yet current in vitro to in vivo extrapolation methods yield poor predictions, particularly for highly protein bound transporter substrates. Explanations for error include inaccuracies in protein binding measurements and the lack of recognition of protein-facilitated uptake, where both unbound and bound drug may be cleared, violating the principles of the widely accepted free drug theory. A new explanation for protein-facilitated uptake is proposed here, called a transporter-induced protein binding shift. High affinity binding to cell membrane proteins may change the equilibrium of the nonspecific binding between drugs and plasma proteins, leading to greater cellular uptake and clearance than currently predicted. The uptake of two lower protein binding OATP substrates (pravastatin and rosuvastatin) and two higher binding substrates (atorvastatin and pitavastatin) were measured in rat hepatocytes in incubations with protein-free buffer vs. 100% plasma. Decreased Km,u values and increased CLint values were seen in the plasma incubations for the highly bound compounds, supporting the new hypothesis and mitigating the IVIVE underprediction previously seen for highly bound transporter substrates.

END OF DAY 2

SATURDAY, JUNE 22, 2019
DDI-2019 - Day 3

7:00 AM – 8:00 AM – REGISTRATION

Session 6: Hepatic versus Extrahepatic DDI
(Chair: Bhagwat Prasad)

8:05 AM – 8:35 AM
Hepatic versus enteric DDI: A comparison of human hepatic and enteric drug metabolism (Albert P. Li, In Vitro ADMET Laboratories LLC, Columbia, MD and Malden, MA) Orally-administered drugs are firstly subjected to first pass metabolism by the enterocytes in the intestinal mucosa. Upon absorption into the portal circulation, the drugs and their enteric metabolites are then metabolized by the hepatocytes in the liver before distribution to the systemic circulation. The parent drugs and their metabolites are further metabolized by all internal organs, with intestine and liver as the most important organs for drug metabolism. In our laboratory, we have optimized cryopreservation of human hepatocytes and have extended the cryopreservation techniques towards human intestinal mucosa. In this lecture, individual and regional differences in the distribution of drug metabolizing enzymes in the small intestine will be detailed and compared to those in human hepatocytes. The activities were quantified using pathway selective substrates for CYPs 1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4; UGTs 1A1, 1A3, 1A4, 1A6, 1A9; SULT; GST; NATs 1 and 2; and aldehyde oxidase.

8:35 AM – 9:05 AM
Quantitative Characterization of UDP-glucuronosyltransferases in Human Liver, Intestine, Kidney, Lung and Heart (Bhagwat Prasad, University of Washington; Seattle, WA) UDP-glucuronosyltransferases are expressed in major drug elimination organs and play important roles in drug disposition, toxicity and efficacy of drugs. In order to develop physiologically-based pharmacokinetics (PBPK) models for UGT substrates, we quantified differential tissue abundance and interindividual variability in UGT abundance in human liver, intestine, kidney, lung and heart. Although major site of UGT expression is the liver, unique abundance profiles of UGTs in intestinal, kidney and lung are critical for the development of the PBPK modeling. Differential regional expression of UGTs in intestinal sections should be considered for the effect of glucuronidation on drug absorption.

9:05 AM – 9:35 AM
Efflux Transporters and Their Roles in Drug-Drug Interaction – Focusing on the Renal Transporters (Yan Zhang, Ph.D., Incyte Corporation; Wilmington, DE) Efflux transporters play an important role in the absorption, distribution and elimination of therapeutic agents and their metabolites. Interruption of the transporter activity may alter the systemic pharmacokinetics and tissue exposure of target drugs, therefore, can potentially lead to organ toxicities. In this presentation, examples of efflux transporter mediated DDI in the liver and kidney will be discussed.

9:35 AM- 10:05 AM – BREAK
10:05 AM – 10:35 AM – SESSION 6 PANEL DISCUSSION

Session 7: Drug Induced Liver Injury (DILI)
(Chairs: Kenneth Brouwer and Kim Brouwer)

10:35 AM – 11:05 AM
Clinical and Mechanistic Evidence for Associations between Drug-Transporter Interactions and DILI: BSEP and Beyond (Kimbrough Brouwer, University of North Carolina at Chapel Hill; Chapel Hill, NC) Transport proteins mediate the hepatic uptake and excretion of many endogenous and exogenous compounds including bile acids, drugs and metabolites. Drug-transporter interactions that disrupt bile acid homeostasis (e.g., BSEP inhibition) have been associated with DILI. Hepatic bile acid transport proteins, including BSEP and O斯塔/β, are tightly regulated to protect hepatocytes from bile acid-mediated toxicity. Gaps in our current understanding of the relationships between drug-transporter interactions, patient susceptibility factors, and DILI risk will be highlighted. This research was supported by NIH R35 GM122576.

11:05 AM – 11:35 AM
Evaluation of BSEP Inhibition and Compensatory Mechanisms in Drug Development (Kenneth Brouwer, BioIVT; Durham, NC) BSEP inhibition is a key initiating step in the development of cholestatic drug induced liver injury. However, the liver has multiple mechanisms to compensate for the increased intracellular concentrations of bile acids resulting from inhibition of BSEP. Methods to evaluate BSEP inhibition and the compensatory mechanisms resulting from inhibition of BSEP will be discussed.

11:35 AM – 12:05 PM
Significance of MDR3 and BSEP Inhibition in Drug-Induced Liver Injury (Kan He, Biotranex; Monmouth Junction, NJ) MDR3 and BSEP are the primary liver transporters involved in bile production by exporting phosphatidylcholine and bile salts, respectively. Phosphatidylcholine and bile salts form mix micelles in bile. Dysfunction of these transporters is associated with wide spectrum of liver diseases. The inhibitions of MDR3 and BSEP activities with drugs associated with liver injury were investigated using the hepatocyte-based assay formats MDR3cyte® and BSEPcyte®.

12:05 AM – 12:35 PM
Identification of DILI Drugs based on Cytotoxic Reactive Metabolites (Albert P. Li, In Vitro ADMET Laboratories LLC, Columbia MD and Maiden MA) Drug induced liver injuries (DILI) continues to be a challenge to the pharmaceutical industry and government regulatory agencies. Routine preclinical and clinical safety trials are not able to identify drugs that would cause serious liver injuries upon exposure to the human population. A review of the literature shows that a large majority of drugs that were identified to cause liver failures were metabolized to reactive metabolites. In our laboratory, we have developed screening assays for cytotoxic reactive metabolites. We propose the following scheme for the identification of drug candidates with DILI potential: 1. Human hepatocyte assay for oxidative stress and cytotoxicity (ROS/ATP assay): In this assay, human hepatocytes are treated with the drug candidates for 48 hrs, followed by quantification of reactive oxygen species (ROS) and cellular ATP contents (ATP), with data expressed the area under the curve (AUC) of the dose response curves of ROS/ATP ratio; using known DILI and non-DILI drugs as calibrators; 2. HEK293/MMHH GSH rescue assay: In this assay, HEK293 cells, a cell line devoid of drug metabolizing enzyme activities, will be used for the quantification of drug cytotoxicity in the presence of a novel hepatic system as an exogenous metabolic activation system, the cofactor-supplemented cryopreserved human hepatocytes (MetMax™ cryopreserved human hepatocytes (MMHH)). Drugs that are rendered more cytotoxic in the presence of MMHH are classified as drugs that are “metabolically activated”. These drugs are then subjected to evaluation in the presence of MMHH with and without GSH supplementation. Cytotoxic drugs with cytotoxicity attenuated by exogenous GSH are classified as drugs forming “cytotoxic reactive metabolites”, and would have DILI potential. The GSH conjugates can be identified to aid structural modification to eliminate the toxicophore.

12:35 PM – 1:05 PM – SESSION 7 PANEL DISCUSSION

1:05 PM
FINAL REMARKS – Albert P. Li, IVAL
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 Thursday, June 14th before the first session begins. 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.

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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.

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- Check in begins at 4:00 pm
- Check out time is 12:00 noon
- Rates are subject to all applicable taxes and assessments; Current tax 15.6% and an amenity fee of $10.00 per room, per night. (Hotel Amenity Fee is Waived)
- The Group Rate shall be offered for a period of three (3) days before and three (3) days after the group dates, subject to availability of rooms at the time of reservation to accommodate those who wish to extend their visits.
- Rates and fees include: SurfPineapple High Band Wi-fi; Bicycles for cruising, In-room coffee and unlimited bottled water, signature pineapple cupcake and coffee Welcome Reception, fitness center, and StreamPineapple.
- Rates are net non-commissionable.

METHOD OF RESERVATION: Individual call-in. Guests must email reservations@staypineapple.com or call 866.866.7977 before Monday, May 19, 2019 to secure their guest rooms. Guests should reference “DDI 2019 - Institute for Scientific Communications” to receive the group rate.

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 20, 2019. Please submit cancellation and refund requests including transferring of registration to: Fax: 410-869-9560; E-mail: nola@ifscomm.org; Cancel Deadline: May 20, 2019

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DDI-2019 Registration Fee Schedule

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