ADDI-2018
Inaugural Asian Conference on Drug-Drug Interactions

December 3-6, 2018
Venue: Lo Kwee-Seong Integrated Biomedical Sciences Building, Area 39, CUHK

REGISTRATION DISCOUNT UNTIL November 3, 2018

Featuring the Following Experts: Albert P. Li; Joan Zuo; Kim Brouwer; Yuichi Sugiyama; Sylvia Zhao; Genfu Chen; Alex Xu; Jingjing Yu; Ming Huang; Sumito Ito; Ryuta Asaumi; Kotaro Nishiyama; Naoki Ishiguro; Guangqing Xiao; Katsuhiko Kanda; Shoko Takeyama; K. Sandy Pang; Kazuya Maeda; Norihiko Iwasaki; Xiaomei Zhuang; Toru Takenaka; Wooin Lee; Nora Lee; Soo-Jin Kim; Li Di; Ru Yan; Chuang Lu; Kenneth Brouwer; Daisuke Tenmizu; Timothy Yung; Ge Lin; Huichang Bi; Chuan Li; Brian Tomlinson; Chonlaphat Sukasem; Yan Zhang, Simon Wong, Jing Lin

ADDI-2018 is an 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

DDI-2018 is sponsored in part by:
CORPORATE SPONSOR

Japanese Drug Metabolism Discussion Group
Mechanisms and Clinical Significance of Hepatic Drug-drug Interactions Involving Efflux Drug Transporters (Kim Brouwer, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA) Transport proteins located on the basolateral and canalicular membranes of hepatocytes mediate efflux from hepatocytes to sinusoidal blood and biliary excretion, respectively, of many endogenous and exogenous compounds, including bile acids, drugs and metabolites. Drug-induced changes (inhibition or induction) in hepatic efflux transporters may impact drug efficacy and/or toxicity. For example, one mechanism of drug-induced liver injury involves disruption of bile acid homeostasis due to impaired bile acid transport. The interplay between bile acid exposure, hepatic transporter dynamics, and the regulation of these proteins will be discussed. Innovative in vitro and in vivo methods to evaluate how drug interactions impact the function of these proteins will be discussed, and the application of mechanistic modeling approaches to improve predictions of hepatic transporter-mediated drug interactions will be highlighted. This research was supported by NIH R01 GM041935 and R35 GM122576.

Extrapolation of In Vitro Drug-drug Interaction Data to In Vivo Clinical Findings (Yuichi Sugiyama, RIKEN Baton Zone Program, RIKEN Cluster for Science, Technology and Innovation Hub, RIKEN; Yokohama, Japan) Recent reports provided quantitative predictions for OATP-mediated DDIs between statins and inhibitors based on PBPK models. 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. The present study aimed to construct a widely applicable method for predicting in vivo DDI from in vitro data.

10:15 AM – 10:45 AM – BREAK

10:45 AM – 11:15 AM

Novel Human In Vitro Hepatic and Enteric Experimental Systems for the Evaluation of Drug-drug Interactions (Albert P. Li, IVAL; Columbia, MD, USA) Drug-drug interactions (DDI) occur as a result of the alterations of metabolic clearance of victim drugs by the perpetrator drugs due to inhibition and induction of uptake, metabolism, and efflux. For orally administered drugs, DDI can occur both in the small intestines as well as in the liver. This lecture will review novel hepatic and enteric in vitro models for DDI evaluation including cryopreserved enterocytes, cryopreserved intestinal mucosa, fully functional 999Elite™ cryopreserved human hepatocytes, as well as permeabilized cryopreserved enterocytes (MetMax™ enterocytes) and hepatocytes (MetMax™ hepatocytes). The strengths and limitations of these systems as well as experimental approach for the evaluation of DDI involving drug transporters and metabolizing enzymes will be discussed.

11:15 AM – 11:45 AM – PANEL DISCUSSION: SESSION 1

11:45 AM – 1:45 PM – LUNCH

Session 1:
Pioneer Lectures: Tools and Experimental Approaches for Assessment of Drug-drug Interactions
(Chair: Joan Zuo, The Chinese University, Hong Kong)

Organizing Chairs:
Albert P. Li, APS Sciences/In Vitro ADMET Laboratories, Inc.
Yuichi Sugiyama, RIKEN Baton Zone Program, RIKEN Cluster for Science, Technology and Innovation Hub, RIKEN
Joan Zuo, The Chinese University, Hong Kong
Genfu Chen, WuXi AppTec
Chuang Lu, Sanofi
Lilly Xu, ChemPartner

Monday, December 3, 2018:
8:00 AM – 9:00 AM – REGISTRATION

9:00 AM – 9:15 AM
Welcome Remarks: Albert P. Li, APS Sciences/IVAL

Session 2:
Clinical Evaluation Drug-drug Interactions
(Chair: Genfu Chen, WuXi AppTec)

1:45 PM – 2:15 PM
IND preparation and submission for both Chinese CDA and USFDA (Alex Xu, CSO of CDE, Chinese Drug Administration)

2:15 PM – 2:45 PM

Drug-Drug Interaction: Clinical Aspects (Sylvia Zhao, China Novartis Institutes of Biomedical Research, Shanghai, China) Emerging new therapies, new drug combinations, and complex treatment algorithms lead to an increasing risk of clinically significant drug-drug interactions (DDI). This talk will give an overview of the new Clinical DDI guidance released by US FDA in October 2017, which is aimed to provide pharmaceutical companies comprehensive guidance on how to evaluate investigational drugs for potential clinical DDIs and drug labeling. The timing of clinical DDI trial, the design and conduct of the studies, the reporting and interpreting of such study results and labeling recommendation will be introduced in the talk. A case study will also be provided to illustrate practical implications.
Mechanistic Analysis of the Risk of Pharmacokinetic Drug-drug Interactions with Drugs Recently Approved by the US Food and Drug Administration (Jingjing Yu, University of Washington; Seattle, WA, USA) This presentation will give a brief review on enzyme- and transporter-mediated drug interaction data for drugs approved by the FDA in the past few years. Key findings from both in vitro and clinical pharmacokinetic-based drug interaction evaluations from New Drug Application reviews will be discussed, highlighting mechanisms and clinical significance.

3:15 PM – 3:45 PM – BREAK

3:45 PM – 4:15 PM
Clinical Trial on DDI Risk Assessment - Case Studies (Min Huang, Sun Yat-sen University, Guangzhou, China)

4:15 PM – 4:45 PM
Translating the In Vitro DDI Properties into Human Drug-drug Interactions Using Physiologically based Pharmacokinetic Modeling (Jing Lin*, Sunovion Pharmaceuticals Inc; Marlborough, MA; Gerald R. Galluppi, Estela Skende, Yu-Luan Chen, Soujanya Sunkaraneni, Kaushik Sarma, Kenneth S. Koblan, Seth C. Hopkins) A physiologically based pharmacokinetic (PBPK) model was established to simulate the pharmacokinetic (PK) profiles and drug interactions of a clinical compound, applying in vitro, preclinical, and clinical data in a middle-out approach. A DDI study in normal healthy volunteers was conducted, and the results are discussed in relation to the PBPK predictions.

4:45 PM – 5:15 PM – PANEL DISCUSSION-SESSION 2
Reception/Vendor presentations: Time TBD
Social event: Reception; Performance by Hong Kong Traditional Dancers

Tuesday, December 4, 2018:
8:00 AM – 9:00 AM – REGISTRATION

Session 3:
Transporter-mediated Drug-drug Interactions (Chair: Yuichi Sugiyama, RIKEN Baton Zone Program, RIKEN Cluster for Science, Technology and Innovation Hub, RIKEN)

9:00 AM – 9:30 AM
The In Vitro Assays for Evaluating BSEP Inhibition Potencies of Drugs (Sumito Ito, Genomembrane, Kanagawa, Japan) The bile salt export pump (BSEP) expressing on the canalicular membrane of hepatocytes mediate the rate limiting step of bile salt efflux from hepatocytes into bile. Impairment of BSEP, followed by cytotoxic bile acids accumulation, has been implicated as a risk factor to cause severe liver injury, and therefore, BSEP inhibitory potential needs to be evaluated at early stage of drug development. The inside-out vesicles isolated from transfected cells are widely used for BSEP inhibition assessment but the utility of double transfected cells created by using a novel transfection system, Opti-expression technology (http://optiviabio.com/opti-expression-transient-expression/), will be discussed.

9:30 AM – 10:00 AM
Predicting Complex DDIs Related to CYP Induction and OATP Inhibition by PBPK Model of Rifampicin with its own Hepatic Uptake and Auto-induction (Ryuta Asaumi, Ono Pharmaceutical, Ibaraki, Japan) This study aimed to construct a comprehensive PBPK model of rifampicin. Namely, multiple aspects of rifampicin pharmacokinetics (saturable hepatic uptake, auto-induction, CYP3A/CYP2C9/CYP2C8/OATP induction, and OATP inhibition) were incorporated into the unified PBPK model. The constructed rifampicin model successfully predicted complex DDIs with glibenclamide (substrate of OATP, CYP2C9 and CYP3A) and repaglinide (substrate of OATP, CYP2C8 and CYP3A) in verification processes. Our established rifampicin model demonstrated the robustness and utility in quantitatively predicting transporter- and metabolic enzyme-mediated DDIs.

10:00 AM – 10:30 AM
Application of PBPK Modeling to Renal OCT2 and MATEs mediated DDIs: Predicting Changes in Renal Clearance and Blood AUC Caused by the Transporter Inhibitors (Kotaro Nishiyama, Nippon Boehringer Ingelheim, Kobe, Japan) Organic cation transporter (OCT) and multidrug and toxin extrusion protein (MATE) are involved in renal secretion of metformin. The aim of this study is to describe DDIs between metformin and OCTs and MATEs inhibitors by using physiologically based pharmacokinetics (PBPK) model.
Factors Influencing Variability of In Vitro Parameters for P-glycoprotein / Breast Cancer Resistance Protein (Naoki Ishiguro, Nippon Boehringer Ingelheim, Kobe, Japan) Drug transporter mediated drug-drug interactions (DDI) are being reported with increasing frequency, thus making it inevitable to study potential interaction during the process of drug development. Recently, regulatory agencies issued (draft) guidance describing target transporters (P-glycoprotein (P-gp)), breast cancer resistant protein (BCRP), organic anion transporter (OAT)1, OAT3, organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE)1, MATE2-K and how to investigate DDIs in vitro, combined with decision trees to judge about the necessity of clinical DDI studies (1), (2), (3). Importance of in vitro transporter data has been increased but it is well recognized that in vitro transporter data (such as inhibition potency (IC50 or Ki) against P-gp and BCRP) shows big inter-laboratory variability with 100-fold (4).

Various points such as experimental systems (Caco-2, recombinant cell system, membrane vesicle etc.), experimental conditions (buffer, albumin, sink condition, sampling volume etc.) and data analysis (efflux ratio, A0iB, B0iB, net transport etc.) have to be considered as reasons why the big inter-laboratory variability was observed. As one of major points, we aimed to compare the IC50 values estimated by different data analysis approaches (5). Transcellular transport of digoxin across Caco-2 monolayer was investigated using various concentrations of three P-gp inhibitors. To calculate IC50 values, three traditional parameters were used: apical-to-basal (A0iB) and basal-to-apical (B0iB) clearance (CL) with inhibitors (CLAt0Bi and CLB0tAi), and the difference between the efflux ratios (ERs) with P-gp inhibitors (ERi) and those under complete P-gp inhibition [ERi-(P-gp)]. Furthermore, a new model-based approach was applied that uses the difference between the reciprocals of CLAt0Bi with P-gp inhibitors (1/CLAt0Bi) and those under complete P-gp inhibition [1/CLAt0Bi-(P-gp)] as parameters. IC50 values obtained from 2 model-based approaches [ERi- ERi-(P-gp) and 1/CLAt0Bi-1/CLAt0Bi-(P-gp)] were comparable, whereas 2.6- to 6.6-fold larger IC50 values were estimated from empirical approaches (CLAt0Bi and CLB0tAi). The reason for such difference in IC50 values is that indicators for model-based approaches, but not empirical approaches, directly reflect the P-gp function. In the presentation, I will touch not only impact of data analysis on in vitro P-gp/BCRP parameters but also those of experimental conditions and systems and discuss how we can tackle with the large inter-laboratory variability of in vitro parameters for P-gp/BCRP.

Hepatocellular Disposition Profiling of Rosuvastatin and Pitavastatin in Sandwich-Cultured Human Hepatocytes: (Katsuhiro Kanda, Hitachi High-Technologies Corporation, Ibaraki, Japan) The hepatocellular disposition profiles of rosuvastatin and pitavastatin in sandwich-cultured human hepatocytes were simultaneously evaluated by the systematic methodology called D-PREX. Ko143 (a strong inhibitor for BCRP) treatment reasonably showed significant decrease in
biliary excretion of both rosuvastatin and pitavastatin. Interestingly, basolateral efflux of rosuvastatin also represented significant transport inhibition by Ko143.

3:00 PM – 3:30 PM – PANEL DISCUSSION-SESSION 3

Social event: Tour of Chinese University of Hong Kong
Free afternoon

Wednesday, December 5, 2018
8:00 AM – 9:00 AM – REGISTRATION

Session 4:
Drug Metabolizing Enzyme-mediated Drug-drug Interactions
(Chair: Chuang Lu, Sanofi)

9:00 AM – 9:30 AM
PBPK Modeling to Describe DDI in Intestine vs. Liver Drug Removal (K. Sandy Pang, University of Toronto, Toronto, Canada) The intestine and liver are two important first-pass removal organs. For drugs that are metabolized by both the intestine and liver, it is notable that the blood flow to the enterocyte region where the enzymes and transporters are housed, is segregated, constituting only < 20% of the total intestinal flow. However, for drugs given orally, the entire dose needs to traverse the intestine. Hence, the segregated flow pattern of the intestine results in route-dependent intestinal removal, with the intestinal playing a more important role for orally administered drugs. This constitutes route-dependent metabolism for both the intestine and liver. DDI will also change according to the route of administration of both perpetrator and victim drug.

9:30 AM – 10:00 AM
Use of Cluster Newton Method to Obtain Reliable In Vivo Ki Values by Analyzing the Change in Pharmacokinetics of both Parent and Metabolites of Victim Compound (Kazuya Maeda, The University of Tokyo, Tokyo, Japan) We tried to perform an accurate simultaneous estimation of “in vivo” inhibition constants (Ki) of inhibitors and fraction metabolized (fm) of substrates, which are important for the precise DDI prediction, from human clinical pharmacokinetic (PK) data by a novel method with Cluster Newton Method and metabolite PK information. In many cases, inclusion of substrate metabolite information in PBPK analysis improved the reliability of both Ki and fm. A large discrepancy was observed between the reported in vitro Ki values and the current in vivo Ki estimates. These results demonstrated that better utilization of substrate metabolite information in PBPK analysis of clinical DDI data can improve reliability of top-down parameter estimation and prediction of untested DDIs.

10:00 AM – 10:30 AM
Assessment of CYP1A2 Inductive Potential of Edaravone, a New Drug Approved for ALS, and Necessity Judgment of the Clinical DDI Study (Norihiko Iwazaki, Mitsubishi-Tanabe Pharma Corporation, Saitama, Japan) Edaravone, a newly approved drug for amyotrophic lateral sclerosis (ALS), has been shown to induce CYP1A2 in an in vitro study using primary human hepatocytes. Riluzole, which is widely used to treat ALS, is mainly metabolized by CYP1A2. Therefore, based on the in vitro basic and mechanistic static model (FDA Guidance, 2012), there exists the possibility of a drug–drug interaction (DDI) risk owing to CYP1A2 induction caused by the use of edaravone as a concomitant drug, assuming that the magnitude of in vitro and in vivo effects is comparable. In the in vitro study described above, the inductive potential of omeprazole as a positive control for CYP1A2 was significantly higher than that in the in vivo study; therefore, we suspect that the clinical DDI risk is overestimated. However, unlike CYP3A4 induction, there is little information about the correlation between the in vitro inductive potential and clinical DDI risk for CYP1A2 induction. Therefore, we challenged the magnitude of in vivo CYP1A2 induction speculated from in vitro data based on the omeprazole study and concluded that a clinical DDI study of edaravone and riluzole is unnecessary and thus can be omitted. This presentation focuses on the issue of minimizing the overestimation of the need for a clinical DDI study on CYP1A2 induction using edaravone as an example.

10:30 AM – 11:00 AM – BREAK

11:00 AM – 11:30 AM
Heterotropic Activation of CYP3A5 by Icotinib and the Enhancement Effect of Ketoconazole (Xiaomei Zhuang, Institute of Pharmacology and Toxicology, AMMS, Beijing, China) Icotinib, a novel epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) originally developed by Beta Pharma, Inc. (Zhejiang, China), has been approved in China to treat NSCLC. Despite icotinib being a prescription drug, investigation of its pharmacokinetic drug-drug interaction (DDI) has not been extensively conducted. During screening for CYP inhibition potential in human liver microsomes (HLM), heterotropic activation toward CYP3A5 was revealed. Activation by icotinib was observed with CYP3A-mediated midazolam hydroxylase activity in HLM (~40% over the baseline) or recombinant human CYP3A5 (rhCYP3A5) (~70% over the baseline), but not in the other major CYPs including rhCYP3A4. Our results showed the activation was substrate and pathway dependent and observed only in the formation of 1'-OH-midazolam, and not 4-OH-midazolam, 6b-OH-testosterone or oxidized nifedipine. Further, the relative activation was enhanced to ~270% in rhCYP3A5 in the presence of ketoconazole. Kinetic analyses of 1'-OH-midazolam formation showed that ICO increased the Vmax values in HLM and rhCYP3A5 with no
significant changes in Km values. Addition of ketoconazole with ICO alone or ICO plus CYP3cide resulted in an increase in Vmax values and decrease in Km values compared to their controls. This phenomenon may be attributed to a new mechanism of CYP3A5 heterotropic activation, which warrants further investigation.

11:30 AM – 12:00 PM

**Prediction of Time-dependent DDI with CYP3A in the Liver and Intestine Based on the PBPK Modeling and Comparison with Data from Clinical DDI Study** (Toru Takenaka, Taiho Pharmaceutical Co., LTD., Tsukuba, Japan)

Prediction of drug-drug interaction (DDI) magnitude by physiologically-based pharmacokinetic (PBPK) model is being used to support internal go/no-go decision-making in pharmaceutical companies. As a case example, a simple PBPK model constructed to prospectively predict DDI magnitude by our compound which has time-dependent inhibitory potency toward CYP3A will be presented. Subsequent clinical DDI study indicated over-estimation of intestinal CYP3A inhibition, therefore this presentation will also show the refined PBPK model which can successfully recover the observed clinical DDI.

12:00 PM – 12:30 PM – PANEL DISCUSSION SESSION 4

12:30 PM – 2:00 PM – LUNCH SESSION 4

2:00 PM – 2:30 PM

**Target-mediated Drug Disposition in Small Molecule Drugs: Its Role in Atypical Pharmacokinetic Non-linearity and DDI** (Woon Lee, Seoul National University, Seoul, Korea)

Target-mediated drug disposition (TMDD) is well recognized as a source for nonlinear pharmacokinetics of biologics which often interact with high-affinity, low-capacity targets. The impact of such TMDD phenomenon was relatively overlooked for small molecule drugs. Considering an increasing drive to achieve high potency and target specificity in small molecule drugs (sometimes via covalent interactions with pharmacological targets), it is important to understand how the saturable interactions of small molecule drugs with their high-affinity, low-capacity targets can generate non-linear and non-stationary pharmacokinetic profiles and impact the risk for drug-drug interactions (DDI). The presentation will cover the recent cases of small molecule drugs displaying TMDD characteristics (using proteasome inhibitor drugs and kinase inhibitors as examples) and their implications in assessing pharmacokinetic profiles and DDI risk.

2:00 PM – 2:30 PM

**Physiologically-based Pharmacokinetic Analysis of Nonlinear Pharmacokinetics of Paclitaxel and Drug Interactions with other Drugs** (Nora Lee, 2, Kota Toshimoto1, Yuichi Sugiyama1; 1Sugiyama Laboratory, RIKEN Baton Zone Program, RIKEN Cluster for Science, Technology and Innovation Hub, RIKEN, Kanzawa, Japan; 2Life Science Research Institute, Daewoong Pharmaceutical, Co., Ltd., Yongin, Korea)

Paclitaxel, known to be a substrate of OATP and mainly metabolized by CYP2C8 has nonlinear pharmacokinetics. To understand the underlying mechanism of the nonlinearity, we established the PBPK model of paclitaxel incorporating binding to cremophor EL (CrEL) micelles, plasma protein and blood cell binding as well as saturable hepatic uptake and metabolism. In our PBPK model analysis, CrEElconcentration was proportional to the paclitaxel dose and was changed in a time-dependent manner. Unbound fraction (fu) of paclitaxel was shown to change in CrEL concentration-dependent manner and was decreased with increasing dose of paclitaxel. Nonlinearity due to the decrease in fu is likely to be an effect of the dose- and time-varying concentrations of CrEL. Besides the effect of CrEL, our PBPK-based analysis demonstrates that Km less than 0.1 μM is required to best describe the nonlinear pharmacokinetics of paclitaxel. Several reports have shown that inactivation of CYP2C8 is associated with adverse events of paclitaxel. CYP2C8*3 is shown to decrease the clearance of paclitaxel by 11% compared to the non-carriers and doubled the risk of grade 2+ neuropathy. Clopidogrel metabolite acyl-β-D-glucuronide, a potent inhibitor of CYP2C8 is associated with increased risk of paclitaxel-induced neutropenia and neuropathy. The PBPK model established in this study will be useful to estimate whether the above described change in side effects by DDI may be explained by PK related DDI or not.

3:00 PM – 3:30 PM

**Recent Advances in Reaction Phenotyping to Access Victim Drug-Drug Interaction** (Li Di, Pfizer Inc., Groton, CT, USA)

Reaction phenotyping is important for drug candidates to access the risk of victim drug-drug interaction potential. Recent advances in methodology will be discussed for challenging compounds. Approaches for non-CYP enzymes, such as carboxyl esterases and reductases, will be highlighted.

3:30 PM – 4:00 PM – BREAK
Interplays of Herbal Medicines with Gut Microbiota Contribute to their Disposition and Efficacy and Interactions with Conventional Medicines (Ru Yan, University of Macau, Taipa, Macao, China) Accumulating evidence support the physiological, pathological as well as pharmacological implications of gut microbiota. The presystemic interaction with gut microbiota, which seems inevitable in traditional oral practice, is essential for determining the in vivo fates and shaping the multi-target holistic actions of herbal medicines (HMs). In this presentation, the gut microbial alteration and how it affects microbial metabolic activity and regulates host intestinal drug metabolizing enzymes and transporters functions will be discussed based on the data obtained from an experimental colitis model. The impact of these changes on the disposition and efficacy of HMs as well as herb-drug interactions will be exemplified with a case study of ginseng.
However, in vitro BSEP IC50 concentrations do not correlate with in vivo cholestatic DILI severity. Sandwich-cultured human hepatocytes (SCHH), when treated with BSEP inhibitors, respond to the resulting increased intracellular concentrations of bile acids (BA), via activation of FXR (adaptive response). This results in decreased synthesis of BA and increased expression of basolateral and canalicular efflux of BA via OStα/β, and BSEP which prevents cholestatic hepatotoxicity. We propose that BSEP inhibition alone may not be sufficient to induce toxicity due to this adaptive response. In addition to BSEP inhibition, inhibition of basolateral efflux and/or interference with the adaptive response (FXR antagonism) may lead to increases in drug-induced cholestatic bile acid hepatotoxicity. Such mechanisms must be incorporated to accurately predict in-vivo cholestatic drug induced liver injury (DILI).

10:00 AM – 10:30 AM

**Case Study for Improvements of CYP DDI Victim Risk GAP between Perspective and Retrospective Prediction Using New ADME Tools, Chimeric Mice with Humanized Liver**

(Daisuke Tenmizu, Astellas Pharma Inc., Tsukuba, Japan)

Case study of compound A will be introduced. The perspective clinical DDI prediction showed the false positive; there was no increase of exposure levels, AUC and Cmax in the clinical DDI study. Subsequently, the additional ADME studies using chimeric mice with humanized liver were conducted and the retrospective clinical DDI prediction showed the good results between predicted and observed exposure levels. We would like to show one of the possibilities how to improve the prediction using new ADME tools, chimeric mice with humanized liver.

10:30 AM – 11:00 AM – BREAK

11:00 AM – 11:30 AM

**Drug-Vitamin Transporter Interaction: Is It Ripe for a Thiamine Transporter (THTR2) Decision Tree?**

(Yan Zhang, Incyte Corporation, Wilmington, DE, USA)

Nutrient transporters including thiamine transporter 2 (THTR2), are regulators of cellular homeostasis that are often overlooked as potential sites for drug-drug interactions during drug development. Data obtained during development of fedratinib, a JAK2 inhibitor for treatment of myelofibrosis, provides a unique example that highlights the critical need to consider interactions with such transporter when assessing potential drug safety and/or toxicity. THTR2 facilitates oral absorption of dietary thiamine. Therefore, inhibition of intestinal thiamine absorption through THTR2 inhibition, on a chronic basis, may lead to thiamine deficiency (TD) and consequently a potential risk of developing Wernicke's encephalopathy (WE). Although several nutrient transporters have been discussed in the recent years, THTR2 will be the focus in the current presentation. The common substrates and inhibitors are among the topics to be discussed including some of the recent publications. The risk factors which may contribute to TD and/or WE will also be included in the presentation. In addition, some of the in vitro and in vivo models to study the functions of THTR2 are updated and compared. Most recently, THTR2 has become one of the emerging transporters appeared in the newly published ITC White paper. With the current available preclinical investigations and clinical observations, whether this is ripe for a broad recommendation for THTR2 and how to extrapolate inhibition risk will be discussed.

11:30 AM – 12:00 PM

**Preclinical Evaluation of Drug-Drug Interaction Potential in Drug Discovery: Challenging the Status Quo**

(Simon G. Wong, Genentech, South San Francisco, California, USA)

Evaluation of drug-drug interaction (DDI) potential has become a key component of the drug discovery screening paradigm in the pharmaceutical industry. Prior to lead optimization, new chemical matter is routinely screened in a high-throughput format for the potential to cause competitive or time-dependent inhibition (TDI) of CYP isoforms, or alternatively, induce CYP isoforms through recognized mechanisms (PXR,Ahr, CAR). The output from these assays facilitates rank order or compound binning based on the anticipated DDI risk, and is not suitable for more comprehensive risk assessment through steady-state or physiologically-based approaches. Nonetheless, the temptation exists to connect the outputs from these higher throughput assays to a more tangible risk assessment. For example, several laboratories have presented good correlations between a shifted IC50 (30 minute pre-incubation) and the commonly used parameter of TDI risk, kinact/KI. Our analysis, however, revealed this correlation is strengthened the presence of compounds with potent and efficient TDI, and a much weaker correlation exists for moderate and weak TDI compounds. This presentation will re-examine the format and application of early readouts for DDI risk assessment and explore alternative methodologies to categorize compounds based on their potential to cause a clinical DDI.
A Pragmatic Approach to Review Herb-drug Interactions for Implementation of Integrative Medicine (Timothy Yung, Hospital Authority of Hong Kong, Hong Kong, China)

Beneficial Herb-drug Interaction in the Combinational Use of Herbal Polyoxypregnanes with Paclitaxel (Ge Lin, The Chinese University of Hong Kong, Hong Kong, China) Medicinal herbs are often concurrently administered with orthodox drugs for the treatment of varieties of diseases to produce beneficial outcomes via herb-drug interactions. However, because of the unique nature of medicinal herbs, which contain multiple ingredients to interact with multiple targets leading to different bioactivities, the investigation of herb-drug interactions and their mechanisms underlying such interaction are challenging. To date, the investigation with sound scientific evidences supporting the beneficial clinical outcomes of such combinational usefulness are far from satisfactory. In the recent years, our research team has been working on herb-drug interactions using our established integrative PK/PD multidisciplinary approach. In this presentation, using one Chinese medicinal herb Marsdenia Tenacissima as an example, our integrative approach for investigating the beneficial herb-drug interaction of herbal polyoxypregnanes with paclitaxel and the underlying mechanisms will be illustrated. Our study identified the true bioactive polyoxypregnanes, which do not directly produce any pharmacological actions, rather serve as “pro-bioactive” components to elicit their bioactivities after biotransformation in the body, and also delineated the mechanism of polyoxypregnanes-facilitating anticancer effects of paclitaxel via their beneficial interactions.

Herb-drug Interactions – Do they Matter in the Clinic? (Brian Tomlinson, The Chinese University of Hong Kong, Shatin, Hong Kong, China) Many herb-drug interactions have been identified by in vitro studies and specific in vivo interaction studies but relatively few are important in clinical practice. Drugs with a narrow therapeutic range such as warfarin are most likely to exhibit significant clinical interactions with herbal materials. However, it is important to consider potential interactions of herbs with any drug where change in systemic exposure may lead to treatment failure or toxicity.
SEE TRAVEL INFORMATION AND REGISTRATION FORM BELOW

FEATURED EXHIBITORS

![IVAL Logo](image)

![PhoenixBio Logo](image)
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 November 3, 2018. 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 schedule. All posters will remain displayed throughout the conference. Please be prepared to display your poster during registration on Monday, December 3, 2018 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.

The conference will be held at

Venue: Lo Kwee-Seong Integrated Biomedical Sciences Building, Area 39, CUHK

TRAVEL INFORMATION:

ISC, Inc. has reserved a special rate at the HYATT REGENCY HONG KONG, SHA TIN: 18 Chak Cheung Street, Sha Tin, New Territories, Hong Kong for the inaugural ADDI-2018 conference to be held at the Lo Kwee-Seong Integrated Biomedical Sciences Building, Area 39, CUHK

Please use this link to make reservations:

https://www.hyatt.com/content/propertywebsites/hotels/regency/shahr/en/group-booking/shahrsc292018.html

Group Date

Thursday, 29th November 2018 – Wednesday, 05th December 2018

Group Rates

1 King Bed / 2 Twin Beds:
HK$1,260 for single with daily buffet breakfast at Cafe for one person
HK$1,380+10% for double with daily buffet breakfast at Cafe for two persons

1 King Bed Harbour View / 2 Twin Beds Harbour View:
HK$1,560 for single with daily buffet breakfast at Cafe for one person
HK$1,680 for double with daily buffet breakfast at Cafe for two persons

* 1 King Bed Harbour View Club Access / 2 Twin Beds Harbour View Club Access:
HK$2,040 for single occupancy
HK$2,340 for double occupancy

* Includes our Regency Club benefits.

The above room rates are subject to 10% service charge per room per night. Wired and wireless Internet access is complimentary. Premium Internet Plan is available at a charge.

Guarantee Policy:

Credit Card guarantee is required at time of booking.

Cut-Off Date:

Thursday, 8 November 2018. Reservation requests received after the cut-off date will be based on availability at the Hotel’s prevailing rates.

Cancellation Policy:

– Cancellation or amendment of stay must be made before 48 hours prior to arrival, otherwise a penalty of one night accommodation charge will be applied.
– No-show on the specified date of arrival will be subject to full room charges for the entire stay.

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 November 3, 2018. Please submit cancellation and refund requests including transferring of registration to: Fax: 410-869-9560; E-mail: nola@ifscomm.org; Cancel Deadline: November 3, 2018

Registration Form AVAILABLE ONLINE AT WWW.IFSCOMM.ORG Email to nola@ifscomm.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 or credit card. Checks should be made 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@ifscomm.org or phone (410) 869-9166; or visit http://www.ifscomm.org.
REGISTRATION FORM: ADDI-2018

Or please register online at: http://www.ifscmm.org/

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. $ __________________________

ADDI-2018 Registration Fee Schedule

Academic and government institutions receive 50% discount per person
Exhibiting companies receive a 50% discount per person
(With a paid Exhibitor registration)

<table>
<thead>
<tr>
<th>Event Name</th>
<th>Registration Fee</th>
<th>Registration Fee</th>
<th>Exhibitor Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDI-2018</td>
<td>$500.00</td>
<td>$625.00</td>
<td>$2,000.00</td>
</tr>
<tr>
<td>ACADEMIC OR GOVERNMENT DISCOUNT</td>
<td>$250.00</td>
<td>$312.50</td>
<td>$1,000.00</td>
</tr>
</tbody>
</table>

B. Registrant Information:

Dr.__________ Mr.__________ Ms.__________
Please type your name as you wish it to appear on your name badge
PLEASE PRINT

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
<th>Mid. Initial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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