ISSX Transporters Focus Group Newsletter

DECEMBER 2020

The ISSX Transporters Focus Group (TFG) is chaired by Xiaoyan Chu of Merck and co-chaired by Xinning Yang of the FDA. The goals of this focus group are to disseminate and promote state-of-the-art research and foster collaborations among ISSX members on the role of transporters in drug disposition, drug interactions, efficacy, and toxicity, and their impact on drug discovery, development, and regulatory decision-making. The ISSX TFG will engage ISSX members throughout the year via webinars, workshops, and meeting planning.

International Society for the Study of Xenobiotics (ISSX)

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Contents

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Update on ISSX TFG Activities

By Dr. Marilyn Morris

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While the 2020 ISSX meeting in Hawaii was cancelled, the TFG has been busy with starting a newsletter, organizing webinars, and submitting program proposals for the 2021 North America ISSX Meeting. The first newsletter was sent out to members in June, 2020, and included highlights of recent publications and an update on NMEs approved by the FDA Jan-June 2020.

This is the second newsletter of 2020 and focuses on activities from July to Dec 2020.

2020 ISSX Webinars Organized by the TFG

- **Update on FDA's Final Drug-Drug Interaction Guidance**
  Presented by: Xinning Yang, PhD, US FDA, June 30, 2020

- **Induction of Drug Transporters *in vitro* and *in vivo*: from Gut ABCs to Liver SLCs and Back Again**
  Presented by: David Rodrigues, PhD, Pfizer, September 15, 2020

- **Modelling and Simulation to Support Qualification of Endogenous Transporter Biomarkers: Current State**
  Presented by: Aleksandra Galetin, PhD, University of Manchester, October 21, 2020

- **Measurement and Quantitative Characterization of Protein Therapeutics Transport Across the BBB and BCSFB**
  Presented by: Dhaval K. Shah, PhD, University at Buffalo, December 15, 2020

Update on ISSX TFG Activities

Contributed to Design and Plan of Scientific Programs

- We held a joint symposium (September 23, 2020) with the American College of Clinical Pharmacology (ACCP) at the 2020 annual meeting of ACCP: Transporter-mediated Drug-Drug Interactions, Current Status & Future Perspectives. Speakers from academia, industry, and different regulatory agencies shared their expert views. The contents of the presentations were connected nicely and covered several active topics in the transporter field. The symposium was well attended with excellent feedback from the audience.

- We submitted several proposals for the programming of the 2021 North American ISSX Meeting, and the following were accepted; Symposium: State of the Art Strategies to Enhance Brain Penetration of Small Molecules and Therapeutic Proteins; Short-Course: Application of Regulatory Guidances for Transporter Related DDIs.

Highlight of Recent Publications

Transporter endogenous biomarkers: What is new in 2020?

Endogenous Biomarkers for OATP1B Transporters

By Drs. Xiaoyan Chu and Hong Shen

In the past few years, there has been rapid and significant progress in the identification and characterization of endogenous biomarkers to assess DDI potential for hepatic organic anion transporting polypeptides OATP1B (OATP1B1 and OATP1B3). In 2020, continued efforts have been made to identify sensitive and selective OATP1B biomarkers, understand the translation of biomarker data to clinical drug-drug interactions (DDIs) with various probe drugs, and explore their utility in predicting DDIs in diseased populations and evaluate complex DDIs, leading to better strategies for DDI management.

Pharmacogenomic studies are powerful tools to identify specific OATP1B biomarkers. In a microarray-based genome-wide association study, the SLCO1B1 rs4149056 (c.521T>C, p.Val174Ala) variation showed the strongest association with the plasma glycochenodeoxycholate and glycodeoxycholate 3-O-glucuronide (GCDCA-3G and GDCA-3G) concentrations (Neuvonen et al., 2020). The mean plasma concentration of GCDCA-3G and GDCA-3G was 9.2- and 6.4-fold higher in individuals with the SLCO1B1 c.521C/C genotype than in those with the c.521T/T genotype. These data, together with in vitro studies indicate that the hepatic uptake of GCDCA-3G and GDCA-3G is predominantly mediated by OATP1B1. GCDCA-3G, in particular, is a highly sensitive and specific OATP1B1 biomarker in humans. Likewise, a large scale pharmacogenomic study measured plasma coproporphyrin-I (CP-I), a sensitive and specific OATP1B biomarker, in 391 Japanese subjects (Suzuki et al., 2020). The results confirmed the utility of plasma CP-I as an endogenous biomarker for phenotyping of OATP1B activity and is potentially useful for the study of DDIs via OATP1B inhibition or individual dose adjustment of OATP1B substrates. Furthermore, a few examples have been published to illustrate the utility of CP-I in drug development to derisk OATP1B-related DDIs and understand the mechanism of complex DDIs for glecaprevir (Kalluri et al., 2020), probenecid (Zhang et al., 2020) and fenebrutinib (Jones et al., 2020). In addition, 28 potential OATP1B endogenous substrates were evaluated for their sensitivity to study OATP1B DDIs in

a rifampin dose-dependent DDI study (150, 300, and 600mg single doses) in human (Mori et al., 2020b). CP-I, direct bilirubin, GCDCA-3G, GCDCA-3S, and hexadecanedioate demonstrated higher sensitivity than others for rifampin dose-dependent change and correlation with several OATP1B probe drugs (atorvastatin, pitavastatin, rosuvastatin, and valsartan). Moreover, a minimal physiologically-based pharmacokinetic model of CPI was developed and three covariates (i.e., decreased hepatic CPI uptake in 521CC relative to 521TT, Asian-Indians relative to Caucasians, and lower CPI synthesis in females relative to males) were identified (Takita et al., 2020a). These studies maximize the sensitivity of CPI to evaluate OATP1B interaction potential as early as in first-in-human studies and to facilitate the design of prospective interaction studies with clinical probes.

Evaluation of OATP1B biomarkers has been extended to diseased populations. Renal impairment (RI) is known to influence the pharmacokinetics of non-renally eliminated drugs, although the mechanism and clinical impact is still not fully understood. The impact of RI and single oral dose rifampin on eight OATP1B endogenous biomarkers (including bilirubin, CP-I, CP-III, and sulfated bile salts) and a microdose probe drug cocktail for CYP3A, OATP1B, P-gp, and BCRP was evaluated in the patients with mild, moderate, and severe RI (Tatosian et al., 2020). The results indicated that rifampin effects on these biomarkers in RI patients were comparable to those in healthy volunteers, which is the first demonstration of the utility of endogenous biomarkers to assess OATP1B related DDIs in RI patients. In patients with non-small cell lung cancer, plasma exposure of several OATP1B biomarkers significantly increased following administration of paclitaxel, a time-dependent inhibitor of OATP1B (Mori et al., 2020a). This finding suggested that OATP1B biomarkers can address practical and ethical issues in elucidating the risks for OATP1B inhibition for anticancer drugs clinically.

Endogenous Biomarkers for OCT2 and MATEs Transporters

by Drs. Xinning Yang and Marilyn Morris

Organic cation transporter 2 (OCT2) and multidrug and toxin extrusion protein 1/2-K (MATE1/2-K) mediate active renal secretion of some endogenous substrates and a number of drugs. Inhibition of these transporters may decrease clearance of substrate drugs. Unbound maximal plasma concentration ($C_{max,u}$) of an inhibitor divided by its IC_{50} against OCT2 or

Highlight of Recent Publications

MATEs is recommended in the regulatory guidance for predicting clinical DDI potential from in vitro results. A recent study examined 20 inhibitor drugs to assess the translatability of this approach based on in vitro IC_{50} values measured with metformin as the substrate and metformin AUC changes from clinical DDI studies (Mathialagan et al., 2020). The analysis suggested that DDI risk may be indicated by considering OCT2 inhibition alone, while MATEs inhibition data lead to good sensitivity but poor specificity for prediction of DDI potential. The analysis also suggested that there is a substantial false positive prediction using the current approach in the regulatory guidance (OCT2 and MATEs $C_{max,u}/IC_{50}$ ratio > 0.02 or >0.1). Thus, the authors proposed that, when the in vivo DDI risk cannot be ruled out using the current approach, the DDI risk can be further assessed by examining the effect of an inhibitor drug on endogenous substrates of OCT2/MATEs such as creatinine and N1-methylnicotinamide (NMN). Evaluating the changes of these biomarker levels from early clinical studies may serve as an additional filter to reduce false positive predictions. NMN may be superior to creatinine due to its higher fraction of active renal secretion in its renal clearance (CLr) compared with creatinine. The results of this study showed the IC_{50} values measured using NMN generally are comparable to those obtained with metformin with less substrate-dependence for MATEs than OCT2.

The utility of NMN as an endogenous biomarker has been demonstrated in the past and is further evaluated in a recent study conducted in healthy subjects who received a series of doses (10 mg, 25 mg, and 75 mg) of pyrimethamine, a known inhibitor of OCT2 and MATEs (more potent towards MATEs than OCT2). Metformin was also included as a reference. The results showed a significant correlation of the change of CLr (expressed as CLr ratio in the presence of pyrimethamine vs. absence of pyrimethamine) between the NMN and metformin, while poor correlation for creatinine vs. metformin is likely due to the limited magnitude of creatinine CLr changes. This study also demonstrated the utility of a novel biomarker, N1-methyladenosine (m^1A), which is a modified nucleoside that originally presents at position 58 in transfer RNA (tRNA). m^1A is a substrate of OCT2 and MATE-2K, but not MATE1 (Miyake et al., 2019). The change of m^1A CLr has a significant correlation with that of metformin. An advantage of m^1A as a biomarker is that its plasma concentration profile had less diurnal variation than NMN. It should be noted that the AUC of m^1A and NMN were not increased along with their CLr reduction in the presence of pyrimethamine. Thus, the results suggested

that urine sample collection is needed to use them as biomarkers for MATEs transporters. While creatinine has low sensitivity as an endogenous biomarker for OCT2/MATEs, it is still routinely measured in clinical studies. Serum creatinine (sCr) levels can be increased by drugs that are inhibitors of OCT2 and/or MATEs and sometimes the elevation of sCr is misinterpreted as a signal indicating kidney injury. Recently, mechanistic models were developed to predict creatinine-drug interactions of 10 OCT2/MATEs inhibitors with consideration of inter- and intra-individual variability of sCr (Scotcher et al., 2020). Two models were developed, assuming either unidirectional or bi-directional OCT2 transport. The models showed comparable performance in prediction of steady-state or maximal percentage change in sCr levels, with the bi-directional OCT2 transport model being able to avoid over-prediction of the effect of ranitidine. Both models were further used to predict creatinine-drug interaction in chronic kidney disease (CKD) populations for cimetidine, famotidine, and trimethoprim which had relevant clinical data available (Takita et al., 2020b). The models generally behaved similarly and well captured the baseline sCr in CKD patients, and 66% of the predicted percentage of increase in sCr with the presence of inhibitor drugs fell within the acceptable prediction limit, with somewhat under-prediction for the effect of cimetidine. Overall, these models enable simulation of dynamics of creatinine-drug interactions over time, and allow differentiation of changes in serum creatinine concentrations due to renal diseases versus inhibition of renal OCT2/MATEs transporters.

Endogenous Biomarkers for OCT1 Transporter

by Dr. Mitesh Patel

Organic cation transporter 1 (OCT1), a facilitative transporter, is expressed on the sinusoidal membrane of hepatocytes and mediates transport of small hydrophilic cationic compounds from blood into the liver. OCT1 has demonstrated emerging relevance in clinical drug PK, PD, DDIs and pharmacogenetic variability. Hence, identification of selective and sensitive OCT1 biomarkers will be valuable in studying the OCT1 inhibitory potential of NMEs in the future. Recently, isobutyryl-l-carnitine has been identified as a potential clinical biomarker for hepatic OCT1 DDIs (Luo et al., 2020). Moreover, a multiplexed HILIC-MS/HRMS method, capable of simultaneously quantifying plasma levels of isobutyryl-l-carnitine, thiamine, NMN, creatinine, carnitine, and metformin, to elucidate clinical inhibition of OCT1/2 and MATE1/2K by NMEs has been established.

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Highlight of Recent Publications

Scotcher D, Arya V, Yang X, Zhao P, Zhang L, Huang SM, Rostami-Hodjegan A, and Galetin A (2020) Mechanistic Models as Framework for Understanding Biomarker Disposition: Prediction of Creatinine-Drug Interactions. *CPT Pharmacometrics Syst Pharmacol* **9:**282-293.

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Approved NMEs by FDA in Jul-Dec 2020

By Dr. Xinning Yang

There are 27 new molecule entity (NME) products approved by US FDA from June 15th to December 15th of 2020, including 6 monoclonal antibodies, 2 peptides, 2 oligonucleotides, and 2 imaging agents (https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020).

Several post-marketing requirements (PMR) were issued for GAVRETO® (pralsetinib, NDA 211281) to further conduct clinical drug-drug interaction studies related to transporters. Pralsetinib is a kinase inhibitor for the treatment of adult patients with metastatic rearranged during transfection (RET) fusion- positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. One PMR required evaluating the effect of a P-gp inhibitor on the pharmacokinetic (PK) of pralsetinib, and another PMR asked for investigating the impact of a combined P-gp and moderate CYP3A inhibitor on the PK of pralsetinib. The other PMR required assessing the effect of repeated doses of pralsetinib on the PK of transporter probe substrates of P-gp, BCRP, OATP1B1/3, MATE1/2-K. Please refer to this link for the PMRs related to drug-drug interactions (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/213721Orig1s000ltr.pdf).

Preliminary TFG 2021 Objectives

For Feedback from TFG Members

by Dr. Xiaoyan Chu

It has been one year since TFG was first formed. Please join us in celebrating our one-year anniversary! As of now, we have 312 members in TFG. We truly appreciate your support and hope you have fun being members of TFG. Moving forward, the TFG steering committee has discussed our 2021 objectives. We are excited to share our preliminary objectives for 2021 outlined below, and would like to hear your feedback and suggestions.

Host 3-4 Webinars on Transporter-related Topics

- Possible topics include transporter IVIVE, transporter and disease, transporters at Blood-CSF barriers, transporters as therapeutic targets, etc. We will select final topics based on the feedback received from the group and available ISSX webinar slots for 2021.
- To provide more opportunities for young scientists, we are going to organize a special webinar to be presented by graduate students and/or postdoc fellows: topics/selection criteria/presentation format to be determined.

Organize and Host a TFG Meeting at 24th North American ISSX Meeting (Boston, September 12 - 16, 2021)

- Gather feedback from the members on group objectives/activities/future focus.
- Discuss/review general group operating principles.
- Recruit new ISSX TFG steering committee members.

Prepare Newsletters (biannually)

- Share new publications in the field, summarize approved new drugs in US/EU and transporter-related PMR or PMC studies.
- Introduce new members, and highlight key activities of the group and reminder of upcoming activities.

Preliminary TFG 2021 Objectives

Contribute to Design and Plan of Scientific Programs for ISSX Meetings

- Contribute to design/plan scientific programs for the meetings/workshops/symposia organized by ISSX.
- Explore the opportunities to collaborate with other scientific societies (such as AAPS and ACCP), organize joint symposia and workshops on transporter related topics.

Please send us your feedback and suggestions via email (xiaoyan_chu@merck.com and xinning.yang@fda.hhs.gov) by **January 31, 2021**.

Upcoming Event: The ISSX and IQ Virtual Workshop March 2-5, 2021

Please also plan to join us for an exciting virtual workshop, "Translation of *in vitro* ADMET Science to *in vivo*: Current Perspectives and Challenges," jointly sponsored by ISSX and the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ).

This four-day virtual workshop will be held March 2-5, 2021 and will bring together scientists from academia, industry, and regulatory agencies in an interactive format to discuss contemporary topics in applied small molecule enzyme and transporter research (view the program: https://www.issx.org/page/ISSXIQProgram).

Please consider submitting an abstract related to the themes of this workshop to present your work in the virtual poster sessions. Selected abstract authors will also have an opportunity to present and join the panel discussion in the daily sessions (dates for abstract submissions are also outlined: https://www.issx.org/page/ISSXIQAbstractSubmission).