ISSX Transporters Focus Group Newsletter

MARCH 2022

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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Update on ISSX TFG Activities

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By Dr. Marilyn Morris

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 impacts on drug discovery, development, and regulatory decision-making.

This newsletter summarizes activities of TFG from Jan to Dec 2021, highlights recent publications about quantification of drug transporter abundance in blood-brain barrier (BBB), and new molecule entities (NMEs) approved by US FDA during the year of 2021. We also share our 2022 objectives for your input/suggestions.

2021 ISSX Webinars Organized by the TFG

- **The Complex Interplay Between the Solute Carrier Transporters, OCT1, THTR1 and THTR2, in Nutrient Deficiencies and Drug-Nutrient Interactions**
  Presenter: Prof. Kathy M. Giacomini, UCSF, May 11, 2021

- **Prediction of Transporter-mediated PK and DDIs using Mechanistic PBPK Models: Challenges and Opportunities.**
  Presenter: Dr. Bridget L. Morse, Lilly Research Laboratories, September 28, 2021

- **Chemoinformatics and Machine Learning to Understand Drug Transporter Selectivity**
  Presenter: Dr. Sanjay K. Nigam, UCSD, October 26, 2021

- **Mechanistic Insights into the Role of Transporters in Drug Pharmacokinetics, Toxicology, and Physiology**
  Special Webinar presented by graduate students/postdoc fellows: Dr. Zubida M. Al-Majdoub, The University of Manchester, Manchester, United Kingdom; Dr. Tianjing Ren, State University of New York at Buffalo, USA; and Ms. Chitra Saran, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, November 23, 2021

Highlight of Recent Publications

Contributed to Scientific Programs of ISSX Meeting and Workshop

- Short-Course: Application of Regulatory Guidances for Transporter Related DDIs, September 13, 2021, ISSX 24th North American Meeting
- Symposium: State of the Art Strategies to Enhance Brain Penetration of Small Molecules and Therapeutic Proteins, September 14, 2021, ISSX 24th North American Annual Meeting
- Submitted a proposal of short course related to transporters for 2022 ISSX 13th International Meeting
- Worked with AAPS Transporter Focus Group to design and plan scientific program for 2022 AAPS Transporter Workshop co-sponsored by ISSX, Apr 11-13, 2022

Highlight of Recent Publications

Advances in quantification of abundance of drug transporter proteins at the blood-brain barrier in central nervous system (CNS) disease populations

By Dr. Hong Shen

There is considerable interest in the quantification of drug transporter proteins at the blood-brain barrier (BBB) because quantification of drug transporter abundance at the human BBB as well as their modulation in CNS diseases, such as glioblastoma and Alzheimer's disease (AD), is critical to predict the brain penetration of CNS-targeting drug candidates and support dose selection and individualization. Although the last decade has witnessed accelerating proteomic investigation on transporter expressions in the liver, kidney, and intestine, there remains a lack of quantitation data on the transporter protein expressions at the human BBB, especially in patients with CNS diseases. Currently available data on the absolute transporter abundances at BBB that were determined by targeted proteomics, were obtained from only 7 to 12 donors (Uchida et al., 2011, Al-Majdoub et al., 2019), 12 patients with epilepsy orgliomas (Shawahna et al., 2011), and 10 patients with AD or dementia (Al-Majdoub et al., 2019), while there are no data on the absolute transporter abundances in isolated micro-vessels of human glioblastomas.

As an important step towards breaking the cycle of knowledge gaps, the protein abundance of transporters important in the efflux and uptake clearance of drugs across the BBB in matched occipital and temporal brain tissue from 30 healthy adults were quantified (Billington et al., 2019). In addition, Bao et al. (Bao et al., 2020) recently determined the absolute protein expression levels of major drug transporters in the BBB of glioblastomas (N = 47), human (N = 30), rat (N = 10), and mouse brain (N = 10), as well as in the cell membranes of MDCKII cell lines, by using liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based targeted proteomics. In glioblastoma, the expressions of the major efflux transporters P-gp and BCRP as well as claudin-5, GLUT1, and Na/K ATPase were significantly reduced compared to control brains (Bao et al., 2020). Significantly decreased expression of claudin-5, a tight junction marker, suggests that the integrity of the BBB is disturbed whereas markedly reduced P-gp

and BCRP protein expression in glioblastoma micro-vessels implies disrupted biochemical barriers. In addition, the protein abundance of BCRP at human BBB is approximately 2-fold greater than that of P-gp (Bao et al., 2020), indicating that BCRP may play a more important role in drug penetration into human brain than previously thought. Moreover, species-dependent expression of P-gp, but not BCRP, was observed as P-gp protein levels were significantly lower at the human BBB than rodent BBB, while BCRP levels were comparable between species (Shawahna et al., 2011, Uchida et al., 2011, Bao et al., 2020). Although multidrug resistance-associated proteins such as MRP4 play an important role in the transport of CNS drugs in vitro, the MRP4 expression was under the lower limit of quantitation in human, brain, and glioblastoma micro-vessels (Shawahna et al., 2011, Uchida et al., 2011, Bao et al., 2020).

To evaluate whether reduced BBB P-gp activity in AD was caused by decreased P-gp expression at the BBB, Storelli et al. quantified the BBB abundance of P-gp and other drug transporters in gray matter brain micro-vessels in AD (N = 43) and age-matched controls (AMCs) (N = 38) from regions affected by AD (hippocampus and the parietal lobe of the brain cortex) and not affected by AD (cerebellum) (Storelli et al., 2021). Interestingly, the abundance of P-gp in the BBB of the hippocampus and the parietal lobe was similar between AD and AMCs. In addition, gray matter BBB abundance of P-gp was reduced in the hippocampus compared with the cerebellum in both subjects with AD and AMCs (Storelli et al., 2021). As a result, the reduced expression was not AD-related and the observed reduced in vivo cerebral BBB P-gp activity in AD using positron emission tomography imaging cannot be explained by reduced abundance of P-gp at the BBB. Moreover, with respect to the effect of AD on gray matter transporter abundance, like P-gp, lower gray matter BBB abundance of BCRP, OATP2B1, and ENT1 in the hippocampus compared with the cerebellum in both subjects with AD and AMCs was observed in the study (Storelli et al., 2021). Similar to P-gp, they could not find any difference in the abundance of these transporters in subjects with AD in regions affected by AD (hippocampus and the parietal lobe) versus AMCs.

Taken together, drug transporter abundance data at the human BBB is critical to better prediction of drug brain penetration and rational design of therapeutics for efficient delivery of drugs into human brain for CNS targeted drugs and to avoid drug related CNS toxicity.

References:

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Storelli F, Billington S, Kumar AR and Unadkat JD (2021) Abundance of P-Glycoprotein and Other Drug Transporters at the Human Blood-Brain Barrier in Alzheimer's Disease: A Quantitative Targeted Proteomic Study. Clin Pharmacol Ther 109: 667-675. PMID: 32885413

Uchida Y, Ohtsuki S, Katsukura Y, Ikeda C, Suzuki T, Kamiie J and Terasaki T (2011) Quantitative targeted absolute proteomics of human blood-brain barrier transporters and receptors. J Neurochem 117: 333-345. PMID: 21291474

Approved NMEs by FDA in Jan-Dec 2021

By Dr. Xinning Yang

There are 50 new molecule entity (NME) and new therapeutic biological products approved by US FDA in 2021, including 2 diagnostic imaging agents, 7 monoclonal antibodies, 4 peptides, 2 oligonucleotides, 2 antibody-drug conjugates, and 3 other large molecule products (https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2021). Among the NMEs approved, 4 are combinational products.

Twelve post-marketing requirements (PMR) and one post-marketing commitment (PMC) studies were issued:

- Evaluate the effect of approved drugs as inhibitors on the pharmacokinetic (PK) of BCRP substrates in humans (asciminib/SCEMBLIX®, infigratinib/TRUSELTIQ®, mobocertinib/EXKIVITY®, sotorasib/LUMAKRAS®)
- Evaluate the effect of approved drugs as inhibitors on the PK of OATP1B substrates in humans (asciminib/SCEMBLIX®, voclosporin/LUPKYNIS®)
- Evaluate the effect of approved drugs as inhibitors on the PK of P-gp substrates in humans (umbralisib/UKONIQ®)
- Evaluate the effect of approved drugs as inhibitors on the PK of substrate of P-gp, BCRP, and OATP1B in humans (belumosudil/REZUROCK®)
- Evaluate the effect of metabolites of approved drugs as inhibitors on drug transporters in vitro (infigratinib/TRUSELTIQ®, Trilaciclib/ COSELA®)
- Evaluate the effect of BCRP inhibitors on the PK of approved drugs in humans (infigratinib/TRUSELTIQ®)
- Evaluate the effect of P-gp inhibitors on the PK of approved drugs in humans (infigratinib/TRUSELTIQ®)
- Evaluate the effect of CYP3A/P-gp inhibitors on the PK of approved drugs in humans (tepotinib/TEPMETKO®)

Preliminary TFG 2022 Objectives

For Feedback from TFG Members

by Dr. Xiaoyan Chu

It has been more than two years since TFG was first formed. As of now, we have 528 members. We extremely appreciate your support and hope you have fun being members of TFG. Moving forward, we are excited to share our objectives for 2022 outlined below, and would like to hear your feedback and suggestions.

Organization of TFG Steering Committee

- Elect new Co-Chair and Steering Committee Members.

Organize ISSX webinars to discuss emerging topics and state-of-the-art research in transporters

- Continue to provide opportunity for young scientists, by organizing a special webinar to be presented by graduate students and/or postdoc fellows.

Organize/host short course for 2022 ISSX 13th International Meeting

- Transporter Phenotyping: from Qualitative Characterization to Quantitative Prediction.

Connect with Transporters Focus Group members

- Issue group newsletters.
- Host an in-person group meeting during ISSX 13th International Meeting (if the meeting occurs in Seattle, WA).

Please send us your feedback and suggestions via email (xiaoyan_chu@merck.com and xinning.yang@fda.hhs.gov).

Upcoming Event: Drug Transporters in ADME: from the Bench to the Bedside April 11-13, 2022

Please plan to join us for an exciting virtual workshop, "Drug Transporters in ADME: from the Bench to the Bedside," jointly sponsored by American Association of Pharmaceutical Scientists (AAPS) and ISSX.

This three-day virtual workshop will be held Apr 11-13, 2021 and will bring together scientists from academia, industry, and regulatory agencies in an interactive format to discuss contemporary topics in transporter research.

ISSX Members receive the AAPS Member rate to attend! To access the code for your registration discount, please visit https://www.issx.org/page/AAPSWorkshop and log in to your member account to reveal the code.

Please visit the AAPS website for additional information about registration and the workshop agenda: https://www.aaps.org/education-and-research/workshops/transporters.