

ISSX

Biotransformation, Mechanisms, and Pathways Focus Group Newsletter

NOVEMBER 2020

The ISSX Biotransformation, Mechanisms, and Pathways Focus Group (BMPFG) is chaired by Amit Kalgutkar of Pfizer Inc and co-chaired by Valerie Kramlinger of Novartis Institute for Biomedical Research. The goals of this group are to disseminate and promote state-of-the-art research and foster discussion and collaboration among ISSX members on the role of biotransformation in drug design, drug-drug interactions, drug safety, and beyond. In addition to providing a discussion forum, this group will also aim to generate and publish position papers on new vistas in biotransformation science in relation to drug discovery/development. The focus group will engage members throughout the year via webinars, workshops, and by contributing to ISSX meeting planning.

International Society for the Study of Xenobiotics (ISSX)

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Contents

ISSX BMPFG Steering Committee	1
Highlight of a Recent Webinar	4
ISSX BMPFG Activities	6

ISSX Steering Committee

We are pleased to introduce the members of the newly formed ISSX BMPFG steering committee. Starting in 2021, this group will be responsible for the selection of activities, which will be the focus of the BMPFG.



Dr. Deepak Dalvie

Dr. Deepak Dalvie is a Sr. Director in Drug Metabolism and Pharmacokinetics at Celgene. Prior to joining Celgene/Bristol Myers Squibb, he was a Research Fellow at Pfizer Global Research and Development in the Department of Pharmacokinetics, Dynamics, and Metabolism in La Jolla, CA. Deepak received his B.Sc. in Chemistry at the University of Bombay, M.Sc. (Tech) in the Technology of Pharmaceutical and Fine Chemicals, at the University Department of Chemical Technology in India, and his Ph.D. in Medicinal Chemistry at SUNY Buffalo, NY. After a postdoctoral fellowship in the areas of chemistry and metabolism, under the supervision of firstly Professor Richard Sundberg at the University of Virginia and then Professor Neal Castagnoli at Virginia Tech, he joined Pfizer as a research scientist in 1992. His research interests include the biotransformation and bioactivation of xenobiotics and understanding the molecular mechanisms of drug metabolism and metabolic activation. He has authored and co-authored several papers in this area and has published several reviews in these fields. He is an Associate Editor for Drug Metabolism and Disposition and serves on the editorial board of Xenobiotica and Drug Metabolism Reviews. He is also a reviewer of manuscripts for journals such as, chemical research in toxicology, Journal of Medicinal Chemistry and current drug metabolism.



Dr. Carley Heck

Dr. Carley Heck currently works as Senior Scientist in Biotransformation at Pfizer, in Groton, CT, USA. In June 2019, she received her Ph.D. in Pharmacology and Molecular Sciences from Johns Hopkins University School of Medicine for her thesis work in the lab of Dr. Namandje Bumpus, in which she focused on probing the potential role of P450 drug metabolism in the hepatotoxicity of NNRTIs. At Pfizer, she works with drug discovery and development teams to characterize small molecule metabolism in *in vitro*, preclinical, and human clinical samples.



Dr. James O'Neill

Dr. James O'Neill is currently an Associate Director with Charles River Laboratories, Edinburgh, Scotland. He earned his Master's in 'Chemistry with Pharmaceutical Chemistry' at Heriot Watt University, Edinburgh in 2008. Around this time James spent a summer internship with Charles River where he was first introduced to the field of biotransformation.

In 2012, after completing his PhD in Chemistry at Heriot Watt University, James returned to Charles River Edinburgh, where he accepted a graduate position in the Chemistry department. This allowed him to combine his interest in biotransformation and high-resolution LC-MS, with his passion for addressing the analytical challenges which often go hand-in-hand with complex sample types and structural elucidation.

James has since worked closely with a number of leading Agrochemical, Pharmaceutical and Animal Health companies as they seek to out-source their structure elucidation requirements to a regulated contract research organization, in order to bring their products to market.

His current interests include the development of bespoke multidimensional chromatography techniques with radiometric and mass spectrometric detection to assist with sample clean-up and chiral applications.

In 2017, James was promoted to Scientific Manager and in 2020 to Associate Director where he now heads a team of 20 scientists, responsible for all accurate mass and structure elucidation activity on the Charles River Edinburgh site.

Dr. Dian Su is a Senior Scientist in Drug Metabolism and Pharmacokinetics (DMPK) at Genentech. Her research focus has been on ADC/small molecule/peptide DMPK areas mainly in the pre-clinical stage. At DMPK, her primary focus lies in small molecule and peptide drug metabolism in discovery stage. In this role, her responsibilities include: 1) developing new generation assays for metabolite identification (Met ID) to improve the throughput and tackle challenges associated with drug metabolite ID; 2) exploring deep understanding of metabolite formation and biological impact, and establish structure-metabolism relationship (SMR) for drug metabolites. Prior to Feb 2017, Dian was a scientist in the BioAnalytical Sciences-Assay Development & Technology Department (BAS-ADT) at Genentech. In this role, she supported the development of new generation antibody-drug conjugates (ADCs) by using LC-MS strategies to understand ADC biotransformations.



Dr. Dian Su

Before joining Genentech in 2012, Dian held a postdoctoral position at the NIH Proteomics Research Resource for Integrative Biology in Pacific Northwest National Laboratory. She

earned her Ph. D. in Chemistry from Washington University in St. Louis under the direction of Michael L. Gross and John-Stephen A. Taylor.

Dian's critical scientific achievements research resulted in 37 including 12 first/corresponding-authored publications in high impact peer-reviewed journals. She has served as a co-chair for conference workshops/seminars and peer reviewer for several scientific journals.



**Dr. Aaron
Teitelbaum**

Dr. Aaron M. Teitelbaum is a Principal Scientist in the Drug Metabolism and Pharmacokinetics Department at Boehringer Ingelheim Pharmaceuticals. His main responsibility is to direct metabolite identification and biotransformation studies (both preclinical and clinical) in support of small molecule development programs. These studies mainly include metabolite profiling and structure elucidation from *in vitro* human hepatocyte incubations, preclinical 14C ADME, FIH SAD/MAD, and 14C human ADME studies. Dr. Teitelbaum's research interests include understanding chemical aspects of drug metabolism and bioactivation as well as the biosynthesis of metabolites utilizing LC-SPE-NMR technologies. Prior to joining Boehringer Ingelheim, Dr. Teitelbaum earned his Ph.D. in Medicinal Chemistry in 2012 from the University of Minnesota under the direction of Rory P. Remmel. Subsequently, he completed a post-doctoral fellowship at the University of Washington from 2012-2014 under the supervision of Profs. Allan Rettie and Rheem Totah. He then completed a second post-doctoral fellowship at Washington University in St. Louis from 2014-2016 under the guidance of Prof. Evan Kharasch. Aaron's expertise in biotransformation relates to the ISSX BMPFG focus group because of his continued passion for strong collaboration between cross-functional departments, as well as between companies and academia externally, all in the effort to learn, innovate, and plan for the future of biotransformation scientists.



Dr. Rheem Totah

Dr. Rheem A. Totah received her Bachelor's degree from Birzeit University in Palestine and her Ph.D. from the University of Kansas, in Lawrence Kansas, under the supervision of Dr. Robert Hanzlik. Her Ph.D. thesis focused on utilizing peroxidases as model systems to study the mechanism of cytochrome P450 mediated N-dealkylations. She is currently an Associate Professor in the Medicinal Chemistry Department in the School of Pharmacy, Adjunct Associate Professor in Oral Biology, School of dentistry, and an investigator at the Cardiovascular Health Research Unit. Her main research focus is studying the mechanism of extra-hepatic cytochrome P450 enzymes and their potential contribution to disease progression and drug resistance. Her lab also studies the mechanism of P450 inactivation and developing new mass spec techniques to detect heme and protein adduct

Highlight of Recent Presentation

Recently, we sponsored an ISSX webinar entitled “Ozanimod Metabolism – Qualification of Disproportionate Metabolites” by Dr. Sekhar Surapaneni from Bristol Myers Squibb, which was very well attended and generated considerable interest and discussion. A manuscript describing the key findings has also been submitted to *Drug Metabolism & Disposition for consideration as an original research paper*.

The key highlight of the presentation was the *detective* work around ozanimod biotransformation, which led to the characterization of previously undetected metabolites in circulation, and was critical in rationalizing the reason(s) for the incomplete mass balance in human disposition studies. Moreover, the involvement of monoamine oxidase (with known species differences in expression) in the formation of a major ozanimod circulatory metabolite created additional challenges with respect to the qualification of these new metabolites in preclinical species used to study ozanimod toxicity. Clearly, this example speaks volumes on the importance of conducting metabolite-scouting studies in the early phases of clinical candidate development using multiple ascending dose plasma samples.

Access to [slides from this presentation](#) and the [recorded lecture](#) are available to ISSX members through the ISSX website. We encourage you to participate in ongoing discussion on this topic through our [ISSX LinkedIn page](#), which is open to anyone.

Abstract of Sekhar’s presentation:

Ozanimod is a once-daily oral immunomodulator that selectively targets sphingosine 1-phosphate 1 (S1P1) and S1P5 and is approved in the US and EU for the treatment of relapsing forms of multiple sclerosis. Full characterization of drug metabolic pathways and enzymes involved in metabolism is important for understanding clinical safety and efficacy profile of the molecule. *In vitro* and *in vivo* studies were conducted to characterize the metabolism and identify the pathways and enzymes involved in the metabolism. The unique metabolic aspects of ozanimod and characterization and qualification of disproportionate metabolites in safety species will be discussed.

Sekhar’s Bio:

Sekhar Surapaneni is currently Vice President, Nonclinical Disposition and Bioanalysis, BMS and his group is responsible for conducting all drug metabolism and bioanalytical studies in

support of drug development for small molecules, biologics and cellular therapies. Prior to joining BMS, he has about 25 years of experience in drug metabolism and pharmacokinetics area working at Lilly, Abbott, Amgen and Celgene. He received undergraduate training in Pharmacy from BITS, Pilani, India, and PhD in Pharmaceutical Sciences from North Dakota State University.

ISSX BMPFG Activities

ISSX BMPFG LinkedIn Group

After our last newsletter, we have added 170 members to our ISSX BMPFG LinkedIn page. This space was created to allow for discussions between BMPFG members on scientific topics, dissemination of recent publications of interest to the group, advertisement of biotransformation-related seminars and job opportunities, and connection with other members within our scientific community. We invite you to join the group. To do so, look us up “ISSX Biotransformation Mechanisms and Pathways Focus Group” on [LinkedIn!](#)

The Members of the ISSX BMPFG

As of now, we have > 450 members in the ISSX BMPFG. We would like to extend our warmest welcome to all existing and new members! We appreciate your support and hope you enjoy the programming, discussion, and networking opportunities! Please sign up on the ISSX Website if you are interested in joining the focus group. We look forward towards hearing from you on proposals & ideas for the BMPFG to focus on (e.g., meetings/webinars & potential publication topics for the group to consider). To join, please visit www.issx.org/page/fg1.

Engagement and Programming

The ISSX BMPFG is working to increase programming and engagement opportunities, including webinars and discussion content for the LinkedIn group. If you have a proposal for a seminar or a discussion topic, please reach out to Amit or Valerie at BMPFG@issx.org. Additionally, in the fourth quarter of this year, the ISSX Focus Groups will each be forming steering committees to direct programming and contribute content. Keep an eye out for the call for applications!

Call for Ideas

If you would like to start a discussion on a topic on the LinkedIn page, join the [ISSX BMPFG LinkedIn group](#). If you have a paper summary to submit for the next BMPFG newsletter, email Valerie and Amit at BMPFG@issx.org.