ISSX Biotransformation, Mechanisms, and Pathways Focus Group Newsletter

JULY 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)

www.issx.org/page/fg1
information@issx.org

Contents

ISSX BMPFG Chair and Co-Chair

Dr. Amit Kalgutkar
ISSX BMPFG Chair

Dr. Amit Kalgutkar (Chair) is a Research Fellow in Pfizer. He received his Ph.D. degree in Chemistry from Virginia Tech and conducted post-doctoral studies at the Department of Biochemistry, Vanderbilt University, prior to joining Pfizer in 1999. Dr Kalgutkar has ~ 20 years' experience in drug discovery/development, spanning multiple therapeutic areas with over 15 investigational drug candidates nominated for clinical development. Dr. Kalgutkar is an accomplished scientific leader inside Pfizer as well as in the external scientific community with over 170 peer-reviewed papers, reviews and book chapters and 8 issued patents. He is currently on the editorial boards of Dug Metabolism and Disposition and Xenobiotica, and has served two terms on the editorial board of Chemical Research in Toxicology (American Chemical Society). Dr. Kalgutkar also serves as an Adjunct Professor at the Department of Biomedical and Pharmaceutical Sciences, School of Pharmacy, University of Rhode Island.

Dr. Valerie Kramlinger
ISSX BMPFG Co-Chair

Dr. Valerie Kramlinger (Co-Chair) is a principal scientist in the department of Pharmacokinetic Sciences at Novartis Institute for Biomedical Sciences. She earned her Ph.D. in Biochemistry from The University of Minnesota (2013) under the mentorship of Prof. Sharon E. Murphy and carried out postdoctoral research at Vanderbilt University under the mentorship of Prof. F. Peter Guengerich before joining the pharmaceutical industry in 2016. Her research interests primarily focus on mechanistic drug metabolism, application of in vitro approaches to study drug metabolism, mechanisms of cytochrome P450 catalysis and other biotransformation reactions, and generation of chemically reactive metabolites. In addition to her current position at Novartis, Valerie is passionate about bridging the academic/industry divide in drug discovery and development by delivering university lectures and participating in outreach events for graduate students and postdocs who are interested in the pharmaceutical industry.

ISSX BMPFG Activities

ISSX BMPFG LinkedIn Group

To create a space discussion on recent publications, advertisement of biotransformation-related seminars, and connection with other members of the ISSX BMPFG, we have created a LinkedIn group. We invite you to join the group. To do so, look us up as “ISSX Biotransformation Mechanisms and Pathways Focus Group” on LinkedIn!

The Members of the ISSX BMPFG

As of now, we have > 350 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!

Upcoming Webinars

Biotransformation in the Context of Drug Design: Steps Taken to Enhance Drug Properties
Presenter: Dr Cyrus Khojasteh, Genentech
Moderator: Mary (Allie) Schleiff, Fourth-year Doctoral Candidate at University of Arkansas
Time: July 17, 2020 at 2:00 pm ET USA
Registration: https://www.issx.org/page/issxwebinar007172020

Biotransformation (drug metabolism) is one of the main mechanisms used by the body to eliminate drugs. As drug molecules become more complicated, the involvement of diverse drug-metabolizing enzymes increases from P450, UGT, aldehyde oxidase, and beyond. Here we will use our understanding of drug metabolism to enable optimizing and designing drugs. We will discuss available techniques to think through solving metabolism-issues from rates of metabolism to bioactivation.

Ozanimod Metabolism – Qualification of Disproportionate Metabolites
Presenter: Dr. Sekhar Surapaneni, BMS
Moderator: Dr. Amit Kalgutkar, Pfizer
Time: September 21, 2020 at 11:00 am ET USA
Registration: https://www.issx.org/page/ISSXWebinar09212020

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.

Highlight of Recent Publications

The BMPFG would like to highlight recent publications in the field and welcome group members to reach out with literature summaries. Below we highlight four recent publication summaries contributed by BMPFG group members:

Crystalline Sponges as a Sensitive and Fast Method for Metabolite Identification: Application to Gemfribrozil and its Phase I and II Metabolites

Summary by Dr. Chandra Prakash, Agios

Identification and structural characterization of metabolites play major roles in drug discovery and in the development of new drug candidates. Knowledge of metabolic soft spots in an early stage of drug discovery is essential to select compounds with favorable pharmacokinetic credentials and to aid medicinal chemists for rational drug design. A variety of analytical techniques such as nuclear magnetic resonance, infrared, and mass spectrometry combined with wet chemistry and H/D exchange have used for the structural characterization of drug metabolites but sometimes these techniques do not provide complete molecular structures of metabolites. A recent article by Rosenberger et al describes a single crystal X-ray diffraction of crystalline sponges (CS-XRD) being used to identify the structure of gemfibrozil metabolites was published in July issue of Drug Metabolism and Disposition. The results showed that the combination of CS-XRD with MS data offers a great opportunity for scientists in drug metabolism and pharmacokinetics to assess the structure of metabolites produced in low amounts from in vitro studies. The technology is also able to provide information on stereochemistry, offering a significant advantage over other techniques such as MS or NMR. Chandra will be opening a discussion on this article on the BMPFG LinkedIn group page; to participate, join the ISSX BMPFG LinkedIn group page!

The June special issue of the *Journal of Medicinal Chemistry* contains impactful articles that highlight aspects of drug metabolism and toxicology that remain important issues in pharmaceutical discovery and development. We encourage BMPFG group members to browse the issue. Below we highlight three of the articles from that issue:

Twelfth-Position Deuteration of Nevirapine Reduces 12-Hydroxy-Nevirapine Formation and Nevirapine-Induced Hepatocyte Death

Summary by James Driscoll, Myokardia

Nevirapine is prescribed for the treatment of human immunodeficiency virus (HIV) infections and for HIV post-exposure prevention. The drug works as a non-nucleoside reverse transcriptase inhibitor and has been associated skin rash and hepatotoxicity in the clinic. Hepatotoxicity of nevirapine is thought to proceed through P450-based hydroxylation of the twelfth position followed by sulfation, which is either reactive or through a hydrogen atom abstraction (HAT) radical formation. One way to reduce P450 HAT is to replace hydrogen atoms with deuterium atoms known as a kinetic isotope effect. This technique is effective in reducing 12-OH nevirapine formation in hepatocytes from humans and mice when the hydrogens of the methyl group of the twelfth position were replaced with deuterium (12-D3NVP) (Sharma et al., 2013). This article by Heck et al. shows a reduction in 12-OH formation of 12-D3NVP and an increase in other hydroxylated metabolites (metabolic switching). Interestingly, differential effects of protein expression were observed in human and mouse hepatocytes of nevirapine compared to 12-D3NVP. The authors found a 30% reduction in hepatocyte cell death with 12-D3NVP compared to nevirapine treated cells. Deuteration of compounds which are bioactivated via aliphatic hydroxylation could be a potential mitigation strategy.

Emerging siRNA Design Principles and Consequences for Biotransformation and Disposition in Drug Development

Summary by John Davis, Novartis Institute for Biomedical Research

Very interesting manuscript by Humphreys et al. providing a solid background on the therapeutic and SAR strategies used in siRNA drug development and the consequences of these strategies on the assessment of siRNA disposition and biotransformation. In general, the key to a successful siRNA therapy is delivery of the moiety inside the target cell where it can bind with AGO2 the effector protein of the RNA induced silencing complex (RISC) causing downregulation of a specific target RNA. Only a small fraction of the siRNA that is successfully delivered to its target cell ends up bound to RISC with the majority being lost to intact elimination and catabolism. Much remains to be learned for these modalities. For instance, an

ideal PK-PD profile has not yet been established, nor has a consensus been reached on what preclinical species best predict human pharmacology. To address these questions along with many others, comprehensive mechanistic ADME studies must be developed for these modalities and sponsors need to work with regulators to ensure appropriate guidance relevant for siRNA's are instituted.

Metabolism and Bioactivation: It's Time to Expect the Unexpected

Summary by Dr. Kevin Johnson, Genentech

In this publication by Driscoll et al., a diverse set of heteroaromatic rings and aliphatic groups present in the top FDA approved drugs with known bioactivation are presented for a broad audience. While reactive metabolites are often associated with indications of drug induced liver injury (DILI), these chemical moieties "are generally considered acceptable" in terms of risk and structure alert classification. Case studies are discussed, including bioactivation schemes (often complicated), conditions for detection, and simple strategies to mitigate risks. The authors recommend a multidisciplinary approach to identify and reduce the number metabolism related risks for lead compounds, but they reiterate that presence of bioactivation in vitro and in vivo does not guarantee a toxicity finding.

Citations

Driscoll JP, Sadlowski CM, Shah NR, Feula A. Metabolism and Bioactivation: It's Time to Expect the Unexpected. J Med Chem. 2020;63(12):6303-6314. doi:10.1021/acs.jmedchem.0c00026

Heck CJS, Seneviratne HK, Bumpus NN. Twelfth-Position Deuteration of Nevirapine Reduces 12-Hydroxy-Nevirapine Formation and Nevirapine-Induced Hepatocyte Death. J Med Chem. 2020;63(12):6561-6574. doi:10.1021/acs.jmedchem.9b01990

Humphreys SC, Thayer MB, Campbell J, et al. Emerging siRNA Design Principles and Consequences for Biotransformation and Disposition in Drug Development. J Med Chem. 2020;63(12):6407-6422. doi:10.1021/acs.jmedchem.9b01839

Rosenberger L, von Essen C, Khutia A, et al. Crystalline Sponges as a Sensitive and Fast Method for Metabolite Identification: Application to Gemfibrozil and its Phase I and II Metabolites. Drug Metab Dispos. 2020;48(7):587-593. doi:10.1124/dmd.120.091140

Sharma AM, Novalen M, Tanino T, Uetrecht JP. 12-OH-nevirapine sulfate, formed in the skin, is responsible for nevirapine-induced skin rash. Chem Res Toxicol. 2013;26(5):817-827. doi:10.1021/tx400098z

Call for Ideas

To contribute to discussion of these and other publications, 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.