Drug Metabolism and Pharmacokinetics Interest Group Report of the Interest Group Workshop
67th ASMS Conference, June 2 to June 6, 2019 Atlanta, Georgia

Endogenous Biomarkers: Measurement to Predict In vivo Drug-Drug Interactions

The Drug Metabolism and Pharmacokinetics (DMPK) Interest Group (IG) Workshop was held on Wednesday, June 5 from 5:45 to 7:00 pm. Coordinator Jonathan Joseph and Co-Coordinator Brian Rago led the meeting by introducing the session. Approximately 80 scientists attended the workshop demonstrating interest in drug metabolism and pharmacokinetics. An expert panel shared their perspectives to spur discussion on the workshop topic. The strong attendance and active attendee participation in the discussion provide a good endorsement for continuing the DMPK-IG in future years. A brief business meeting was held at the beginning of the workshop to review the status of the current Oral Sessions, solicit ideas for future DMPK Oral Sessions and Workshops, as well as a call for nominees and volunteers for future DMPK-IG sessions. Two new workshop co-coordinators were selected for future years.

1. Review of the DMPK IG Goals

The DMPK Interest Group goals of providing a discussion forum to MS practitioners in drug metabolism, pharmacokinetics, qualitative and quantitative, non-regulated bioanalysis include sharing:

- Recent advances in techniques and methodologies for metabolite identification and pharmacokinetic bioanalysis
- Interpretation of and application of related guidance documents (i.e. MIST, ICH M3, DDI, expl. IND)
- Sharing of best practices across industry and academia
- Provide input on ASMS conference program of interest to scientists working in DMPK
- Reach out and coordinate with related groups to complement scope and broaden outreach to scientific community

2. 2019 and future DMPK IG Coordinators

2019: Jonathan Josephs, Sanofi (Coordinator) - jonathan.josephs@sanofi.com
Brian Rago, Pfizer (Co-Coordinator) - brian.rago@pfizer.com

2020: Brian Rago, Pfizer (Coordinator) – brian.rago@pfizer.com
Aaron Teitelbaum, BI (Co-Coordinator) - aaron.teitelbaum@boehringer-ingelheim.com

2021: Aaron Teitelbaum, BI (Coordinator) - aaron.teitelbaum@boehringer-ingelheim.com
Bhawgwat Prasad, UW (Co-Coordinator) – bhagwat@uw.edu

2022: Bhawgwat Prasad, UW (Coordinator) – bhagwat@uw.edu
Lina Luo, Pfizer(Co-Coordinator) – lina.luo@pfizer.com

3. Update on the DMPK Interest Group's Impact on the 2019 ASMS Program

We thank the ASMS Program Vice President of Programs Richard Yost for being receptive to our requests and proposals for a comprehensive set of DMPK oriented oral sessions for the 2019 meeting. This responsiveness was reflected in the increased number of DMPK oriented Oral sessions and the positive feedback from the Interest Group attendees. The DMPK oriented oral sessions were:

- Mon AM: Biomarkers: Qualitative Analysis
- Mon PM: Therapeutic Proteins, Antibodies, and Antibody/Drug Conjugates
  Biomarkers: Quantitative Analysis

- Tues AM: Imaging: Pharmaceuticals, Metabolites, and Lipids
- Tues PM: Drug Target Identification by MS
- Weds AM: Metabolomics: New Technologies and Applications
  Microdosing and Microsampling: Analytical Challenges
- Weds PM: Ion Mobility: Small Molecules, Pharmaceuticals, and DMPK
- Thurs AM: Drug Discovery and Development: Quantitative Analysis
- Thurs PM: Microorganisms and the Microbiome

4. Suggestions on ASMS 2019 Oral Session Topics from DMPK-IG Attendees

The attendees agreed that the current topics were still of high interest and supported expanding on them on the 2020 program, thus suggested oral session topics for ASMS 2020 are

Proposed Topics for 2020 ASMS	**Proposed Session Time**	**Proposed Session Chair**	**Contact Email/Phone**	**Proposed Backup Chair**
Drug Discovery and Development: Quantitative Analysis	Mon AM	Barry Jones, Q2 Solutions	barry.jones@q2labsolutions.com	Rob Sturm, Zoetis **robert.sturm@zoetis.com**
Biomarkers: Quantitative Bioanalysis	Mon PM	Brian Rago, Pfizer	brian.rago@pfizer.com	
Imaging: Pharmaceuticals, Metabolites, and Lipids	Tues AM	Jose Castro-Perez, Agious	josecastroperez@yahoo.com	
Novel LC-MS Options for Structural Characterization of Drug Metabolites and Impurities	Tues PM	Silvi Chako, BMS	silvi.chacko@bms.com	Donglu Zhang, Genentech
Therapeutic Proteins, Antibodies, and Antibody/Drug Conjugates	Wed AM	Violet Lee, Genentech	lee.manjui@gene.com	
Endogenous Protein Biomarkers in Drug Discovery and Development: Quantitative Analysis	Wed PM	Eric Ballard, Amgen	tballard@amgen.com	
Ion Mobility: Small Molecules, Pharmaceuticals, and DMPK	Thu AM	Fumin Li, PPD	Fumin.Li@ppdi.com	
Precision Medicine and LC-MS	Thu PM	Matt Blatnik, Pfizer	matthew.blatnik@pfizer.com	

Attendees provided many additional suggestions for additional/alternate topics such as:-

Precision Medicine and LC/MS
Tissue Imaging
Exosomes and Drug Disposition
Gene Therapy
Radiolabeled Peptide Studies
Metabolism of New Modalities

As an interest group we wish to continue to work with the ASMS Vice President of Programs to identify potential Oral Session topics and Oral Session Chairs. To support a strong DMPK focus in future ASMS meetings the DMPK IG encourages people to submit DMPK focused abstracts for oral sessions to the 2020 ASMS planning committee.

Based on feedback from Attendees and DMPK IG Members, the DMPK-IG requests returning scheduling the DMPK-IG Workshop to Monday night 5:45 to 7 pm as has been the tradition for many years in the past.

5. Discussion Topic: "*Endogenous Biomarkers: Measurement to Predict In vivo Drug-Drug Interactions"*

Current in vitro models at assessing drug-drug interaction (DDI) liability of a new chemical entity (NCE), though the gold standard in drug discovery, struggle with a high false-positive rate (~30%). The ability to interrogate a validated transporter biomarker, in early clinical studies, such as first-in-human (FIH) studies, would help assess DDI liability, complement the existing agency DDI risk assessment approaches, help confirm or dispute in vitro data and potentially reduce the number of dedicated DDI clinical evaluations. This could result in earlier discharging of DDI risk and lead to significant resource and time savings.

Endogenous biomarkers of CYP and transporter activity have emerged recently as a growing area of interest for biomarker research and may provide insights into the potential for clinical DDIs without the need to conduct a specific clinical trial with a probe substrate. In addition to the traditional CYP enzymes considered. Transporters include OATP1B1/1B3, OCT1, OAT2, NTCP, OCT2, MATE1 and MATE2K. Recently, publications have explored coproporphyrin isomers (CP-I and CP-III), bile acids (BAs), and N1-methylnicotinamide as potential OATP1B1/3 and renal OCT2 transporter biomarkers, respectively. Additionally, thiamine and 6β-hydroxycortisol have been proposed as possible endogenous probes for hepatic OCT1 and renal OAT3, respectively. Creatinine has been proposed as a biomarker for OCT2, MATE1 and MATE2K inhibition.

While using traditional triple quadrupole-based assays for biomarker quantitation has been well demonstrated for a number of these biomarkers. Using UHPLC-HRMS to interrogate potential biomarkers has several advantages: targeted quantitation, multiplexing of biomarkers, and also post-acquisition data mining of novel biomarkers.

An experienced panel offered comments on the current state, their experiences and provided thoughts on where the field is going. Questions from the audience resulted in a robust discussion.

Based on this background the three panel speakers provided their experiences and

recommendations:

1. Discovery and Validation of Pyridoxic Acid as an Endogenous Probe for OAT1 and OAT3 Transporter Function – Petia Shipkova, BMS
2. Multiplexed LC-HRMS/MS assay and Application in Human Plasma as Potential Transporter Biomarker Investigation – Lina Luo, Pfizer, Inc.

3. Bile acid sulfates and glucuronides as a protentional ADME DDI Biomarker – Brian Rago, Pfizer, Inc.

   Following the brief presentations, the audience and Panel Members engaged in an extended discussion with additional viewpoints from the audience adding many points of discussion to the panel members' introduction. The audience interest in this discussion was evidenced by the fact that we had to curtail questions and comments in order for the workshop to finish.

Current Officers for the ASMS DMPK Interest Group:

Jonathan Josephs (Outgoing Coordinator for 2019)
Sanofi
Boston, MA
e-mail: jonathan.josephs@sanofi.com

Brian Rago (Coordinator for 2020)
Pfizer Inc.
Eastern Point Rd
Groton, CT 06340
e-mail: brian.rago@pfizer.com