**Drug Metabolism and Pharmacokinetics Interest Group Report of the Interest Group Workshop 65th ASMS Conference, June 4 to June 8, 2017 Indianapolis, Indiana**

***Hepatocytes: Current and Future Use in DMPK***

The Drug Metabolism and Pharmacokinetics (DMPK) Interest Group Workshop was held on Tuesday June 6 from 5:45 to 7:00 pm. Coordinator Philip Tiller and Co-Coordinator Mark Cancilla led the meeting by introducing the session. Approximately 75 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.

## 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. 2017 and future DMPK IG Coordinators

2017: Philip Tiller, RMI Laboratories (Coordinator) – philip_tiller@rmilaboratories.com
Mark Cancilla, Merck & Co. (Co-Coordinator) – mark_cancilla@merck.com

2018: Mark Cancilla, Merck & Co (Coordinator)
Jonathan Josephs, Thermo (Co-Coordinator)

Attendees will be asked to vote for future coordinators based on a list of volunteers at the 2018 ASMS conference in San Diego

2019: Jonathan Josephs, Thermo (Coordinator)
Co-Coordinator (TBD in 2018)

## 3. Update on the DMPK Interest Group's Impact on the 2016 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 2017 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: Applications of Stable Isotope Labeling
- Mon PM: Analytical challenges of microdosing and microsampling studies & Ion Mobility: Small Molecules, Pharmaceuticals, and DMPK
- Tues AM: Quantitative Analysis in Drug Discovery and Development

- Tues PM: MS in the Regulatory Environment
- Weds AM: N/A
- Weds PM: Antibody and Antibody-Drug-Conjugates
- Thurs AM: Imaging: Pharmaceuticals, Metabolites, and Lipids
- Thurs PM: HRMS for Quantitation in Drug Discovery, Development and Beyond

**4. Suggestions on ASMS 2018 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 2017 program, thus suggested oral session topics for ASMS 2017 are

| Session Title/ Topic | Day/ Time |
|---|---|
| Ion Mobility: Small Molecules, Pharmaceuticals, and DMPK | Mon AM |
| Metabolism/Catabolism of Biotherapeutics | Mon PM |
| Characterizing the ADME properties of biomarkers | Tues AM |
| MS Solutions for Drug Metabolism Challenges | Tues PM |
| Imaging: Pharmaceuticals, Metabolites and Lipids | Wed AM |
| HRMS for Quantitation in Drug Discovery and Development | Wed PM |
| Antibody and Antibody-Drug-Conjugates | Thu AM |
| Intact Mass Analysis for Protein Quantitation | Thu PM |

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

Identification of covalent protein adducts
Metabolism/Catabolism of Biotherapeutics
New methodologies for enhanced small molecule fragmentation
MS in microbiome investigations

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. In order 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 2018 ASMS.

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: "*Hepatocytes: Current and Future Use in DMPK"***

Hepatocytes have become an integral tool in pharmaceutical research. Hepatocytes have been routinely used to generate metabolic stability/ intrinsic clearance and metabolite profile data. These assays are conducted using hepatocytes in suspension and have been, and continue to be effective assays, even though they exhibit a cell viability period of up to only 4 hours.

As more of the new chemicals being synthesized exhibit increased metabolic stability, there is a need to extend the hepatocyte incubation period to afford meaningful data. In recent years several approaches have been developed to increase the viable incubation period, such as hepatocyte relay assays, plated and co-cultured human hepatocyte systems, and these have matured, such as

HepatoPac from Ascendance (Hepregen), Hurel co-cultured primary hepatocytes, 3D hepatocyte sphereoids (Organovo) and the various hepatocyte relay assays (both suspension and plated). Additional in vitro assays have also been explored with these new tools such as toxicology, transporters and biliary excretion. The goal of the workshop was to stimulate a discussion on the use of these new and various hepatocyte platforms in the discovery and pre-clinical arena. A panel of those in the field with hands-on experience 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 four panel speakers provided their expert perspectives:

1. Hepatocyte Relay Method – Phil Tiller
    - Review of novel plated hepatocyte relay assay for in vitro evaluations of slowly metabolizing compounds from Albert Li's paper in Drug Metabolism Letters, 2015.
    - Hands-on experience demonstrated clear advantages to be able to determine Clint and identify metabolites from 4 – 48 hours.
    - Disadvantages were dilution of sample over multiple relays, complex Clint calculations and long assay times (relay needed every four hours)
2. Micropatterned Hepatocyte Co-cultures: HepatoPac (Ascendance/Hepregen) – Ragu Ramanathan
    - Micropattented co-culture (MPCC) is a new in vitro system, which is comprised of a mixture of hepatocytes and fibroblast cells, capable of remaining viable and highly functional for up to 4 weeks.
    - Provides an option to generate metabolites of slow turn over compounds or metabolites formed via multiple steps
    - Demonstrated first time detection and confirmation of the major circulating male rat metabolite of Loratadine and Desloratadine using an in vitro system
3. Hurel® Hepatic co-cultures– Mark Cancilla
    - Provided a head-to-head-to-head comparison of Hurel and HepatoPac hepatocyte co-culture systems against plated hepatocytes with known compounds
    - All metabolites in Hurel at 5 uM were also detected in Hepatopac at 5 uM
    - All systems are appropriate for metabolite ID and Clint purposes. Yet co-cultured systems are superior for low turnover compounds
    - Hurel cost is appropriately equivalent to plated hepatocytes. Reproducibility and QC may be improved from vendor. Cost may fit needs more appropriately for higher throughput organizations.
4. Hepatocyte Spheroid Models and Applications in Drug Metabolism - Jinping Gan
    - Discussed representative formations of human hepatocyte spheroids.
    - Spheroids are viable much longer than other hepatocytes models and the CYP activities were well maintained for CYP1A2 and 3A4
    - Robust metabolic activity was observed with probe substrates of CYP3A, CYP1A, and CYP2B6.
    - The treatment of spheroids for 3 days with prototypical inducers resulted in robust induction of the respective enzyme activities

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:**

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