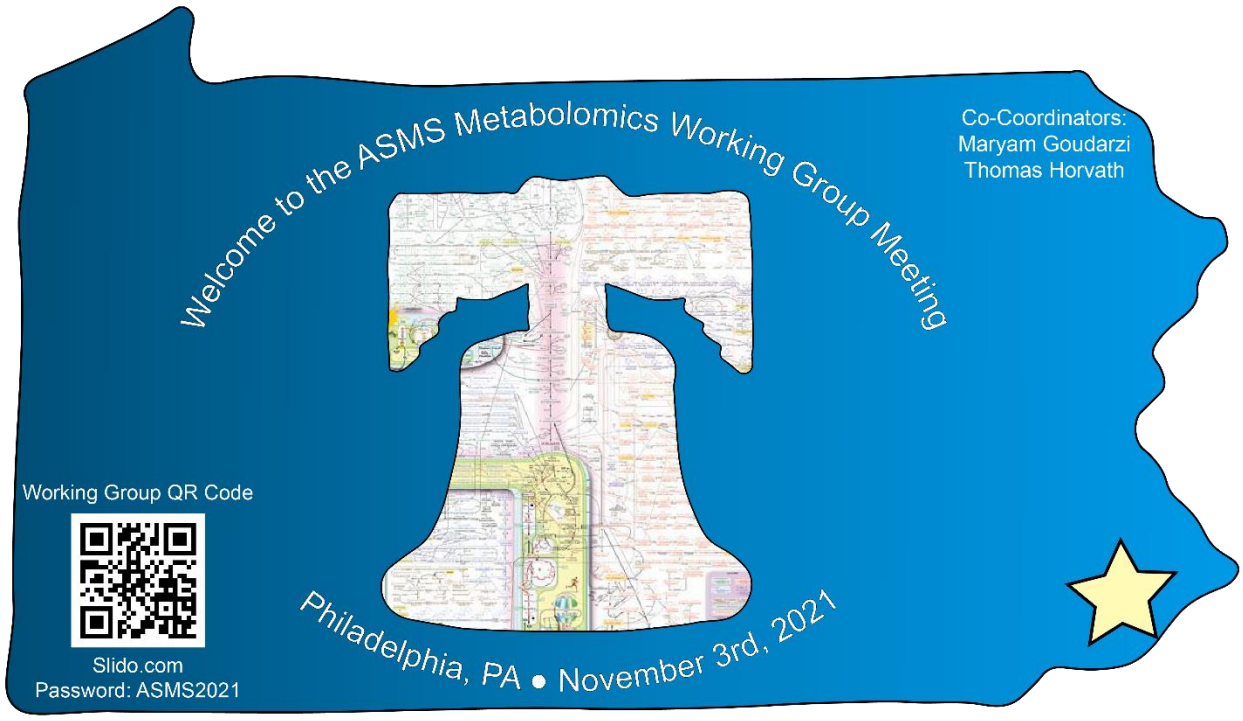
Meeting Co-coordinators:
A.) Maryam Goudarzi, PhD, Cleveland Clinic Lerner Institute
B.) Thomas Horvath, PhD, Baylor College of Medicine & Texas Children's Hospital Microbiome Center

Meeting Logo:



Meeting Overview:

Meeting Title: Metabolomic applications in human health and environmental sciences

Meeting Theme: The meeting coordinators, Dr. Thomas Horvath (Baylor College of Medicine) and Dr. Maryam Goudarzi (Cleveland Clinic) opened the workshop by providing an overview of the workshop's format and theme. This workshop was organized to highlight the metabolomics research of two established investigators, Dr. Douglas Walker (exposomics; Icahn School of Medicine at Mount Sinai) and Dr. Melinda Engevik (microbiome and mammalian gut-brain axis; Medical University of South Carolina) as well as research by 3 early career scientists, Hoda Safari Yazd (PhD Candidate, Florida), Brady Anderson (PhD Candidate, Michigan) and Maxim Seferovic (PhD, Instructor, Baylor College of Medicine). The talks by the early-career scientists were given in a 5-minute lightening talk format and at the end the best presentation was voted on by the workshop attendees. The discussion focused on the direct application of metabolomic techniques in the biomedical and environmental research settings. The speakers encouraged a free-discussion format. The workshop provided an excellent networking opportunity, especially for early-career investigators who made up more than half of the attendees, to gain access to the broad experience base present in the ASMS Metabolomics Interest Group.

Featured Speakers & Their Abstracts:

A.) **Douglas Walker, PhD, Icahn School of Medicine at Mount Sinai**:

Title: Establishing an untargeted framework for the human exposome by high-resolution mass spectrometry

Abstract: Over a lifetime, humans experience thousands of chemical exposures from multiple sources. A more complete estimate of environmental exposures across the lifespan would be a transformative research initiative. The use of high-resolution mass spectrometry (HRMS) provides a key platform for assessing the exposome and provides measures of thousands of chemical signals in a single human sample. Current approaches have increased the ability to measure a wide range of exposures in biological samples, improving potential to capture many of the 200,000 chemicals registered with the EPA, FDA or otherwise used in commercial products. This presentation will discuss the untargeted analytical frameworks adapted from metabolomics analysis to improve measurement of the human exposome. We will highlight recent advances in using multiple untargeted analytical platforms, sample preparation techniques, data processing and annotation strategies to improved capture of exposure biomarkers in human samples. The use of enhanced exposome analytical frameworks based upon untargeted HRMS are poised to provide a robust foundation for exposome research and facilitate development of a knowledge base of environmental chemicals, their products, distributions and associated effects.

B.) Melinda Engevik, PhD, Medical University of South Carolina:

Title: Bifidobacteria and commensal gut microbes shape neurotransmitters levels in the gut and brain during postnatal development.

Background: It is well established that the postnatal acquisition of intestinal microbes significantly influences host health in early life. The microbiome is known to help mature the immune system, protect the host from pathogens, and provide nutrients via the fermentation of non-digestible dietary substrates. However, specific contributions to host health hinge on which species are acquired during this time. Beyond microbial composition, functional features of microbial metabolism are leading to the identification and rediscovery of potentially important bioactive compounds originating from the microbiome. Healthy breast-fed infants are dominated by Bifidobacteria in early life. Bifidobacterial colonization coincides with the window of postnatal neurodevelopment, which makes them attractive models for analyzing how the microbiome affects the gut and brain during development. The central hypothesis of this research is that early Bifidobacteria-host communication impacts neurotransmitter composition in the gut and brain and ultimately affects behavior.

Methods: We colonized neonatal gnotobiotic mice (starting on postnatal day 1) with a simplified model of the human infant gut microbiota consisting of four Bifidobacterium species (B. longum subsp. infantis, B. breve, B. bifidum, and B. dentium). Germ-free (GF) mice and mice neonatally-colonized with a complex, conventional murine microbiota (CONV) served as controls for comparison. Pups were examined at postnatal days P4, P10, and P20. 16S ribosomal RNA gene sequencing characterized the gut microbial communities over-time. Neurotransmitters and bacterial metabolites were examined in the cecum, colon tissue, and brain (hippocampus, cerebellum, and cortex) by LC-MS/MS. At 6-7 weeks of age, mice underwent a behavioral test battery. Results: In early postnatal development (P4 and P10), few neurotransmitters were observed in the gut, but with increased microbial load (P20), we observed increased intestinal neurotransmitters in BIF and CONV treated mice compared to GF controls. Interestingly, we observed unique patterns in the GABA/Gln/Glu cycle, tyrosine and tryptophan pathways in the brain over time; a substantial neurotransmitters being elevated in the CONV mice compared to GF mice. Correlating with these findings, we observed exhibited an upregulation of synapse-promoting genes in several brain regions in CONV and BIF mice. Results from the behavioral tests suggest that GF mice have decreased short-term recognition memory, sociability, anxiety-like behaviors, and motor performance. Postnatal conventionalization rescued these behavioral abnormalities and Bifidobacterial colonization selectively recapitulated the results observed in conventionalized mice. Significantly, Bifidobacteria rescued the recognition memory deficit in germ-free mice.

Conclusion: We propose that Bifidobacteria are key species of the intestinal microbiome which during neurodevelopment promote network refinement and functional organization of neural circuitry, and later in life modulate and maintain healthy brain function.

Early-Career Lightening Talk Speakers & Their Abstracts:

A.) Hoda Safari Yazd, PhD Candidate, Florida (Tim Garrett's Lab):

Title: Mass Spectrometry-Based Multi-Omic Characterization of Meningioma Grades using Machine Learning.

Abstract: Meningiomas are among the most common tumors affecting the central nervous system. The WHO divides meningiomas into three histologic grades: grade I, II, and III which correspond with prognosis and determine therapy. A clear distinction of tumor grades is crucial since the treatment decisions, surgery, and radiation therapy depend on this knowledge. However, at a rate of ~20%, meningiomas with histologic low grade may exhibit clinically aggressive behavior and recurrence, which results in significant morbidity and mortality of affected patients. To date, there are minimal data regarding biomarkers that can be used for early diagnostic and prognostic purposes of meningiomas. Our study aimed to obtain small molecules and lipid species profiles of low and high grades of meningioma brain tissue biopsies using UHPLC-HRMS, and by employing various machine learning algorithms we further characterized possible differences between them, achieved higher specificity in the classification of meningioma, and distinguished potential diagnostic biomarkers.

B.) Brady Anderson, PhD Candidate, Michigan (Robert Kennedy's Lab):

Title: Collection and Utilization of Improved Untargeted Metabolomics Tandem Mass Spectrometry Data

Abstract: The total number of unique metabolites matchable to a spectral database following liquid chromatography tandem mass spectrometry (LC-MS/MS) collection is improved with longer gradient lengths, higher sample loading, and rolling precursor ion exclusion (i.e. "iterative acquisition"). For the analysis of a pooled human plasma extract, 2,052 unique metabolites were identified with the improved LC-MS/MS conditions compared to 214 with a high-throughput and low sample loading method commonly employed for quantitative metabolomics studies. Improvement in compound ID performance was most apparent for low abundance metabolites, but greater quality MS/MS spectra of unknown features was also observed. A localized machine learning model was built to prioritize unknown features that are more likely to be identifiable by MS/MS database matching. The alignment for 68.0% of newly identified metabolites and 63.8% of high-priority unknowns from the improved conditions to a conventional 20-minute LC-MS run was achieved with metabCombiner, increasing the practicality of our approach.

C.) Maxim Seferovic, PhD, Instructor, Baylor College of Medicine (Kjersti Aagaard's Lab):

Title: Fetal-placental exposure to trace bacteria and their bile acid metabolites is modified with treatment of IHCP

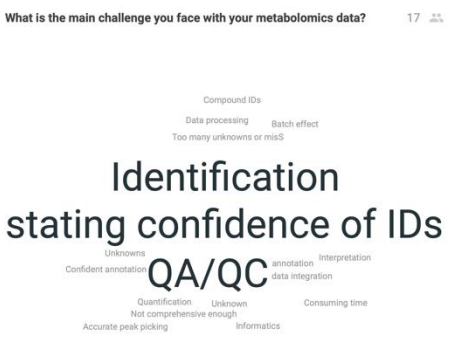
Abstract: Bacterial metabolites and antigens shape fetal immune development trans-placentally. With intrahepatic cholestasis of pregnancy (IHCP) high bile acids are treated with an exogenous xenobiotic bile acid (Ursodeoxycholic acid). Since, bile acids and microbes are mutually influential, we assessed IHCP's effect on fetal exposure. Placentas (n=50) were profiled by MRM assay for 18 bile acids and trace bacterial signatures by metagenomic sequencing. Of nine bile acids significantly increased in IHCP, 7 were microbially derived ($p<0.05$). Hierarchical clustering structured bile acids by IHCP severity, and

Ursodeoxycholic acid treatment ($p<0.01$). Microbial derivatives of Ursodeoxycholic acid correlated to treatment duration ($r=0.30$, $r=0.26$, and $r=0.26$) ($p<0.05$). Metagenomic assessment revealed that placentas of treated pregnancies were taxonomically distinct ($p<0.05$, PERMANOVA). Bacterial bile acid derivatives explained the taxonomical variance (beta diversity PCA correlation $r=0.69$, 0.67, and 0.69) ($p<0.002$). Because of the bidirectional influence of bile acids and microbiomes, IHCP treatment may have consequences immuno-development.

Meeting Summary:

In-person Attendance: The meeting had 20 people in attendance. The online attendees notified us via the chat option of the ASMS program App that there were significant audio and video challenges that persisted over the course of the meeting. The technicians in the room told the coordinators that one of the personal laptops used at the start of the meeting caused an issue with the AV system that ended up disrupting the video feed to the virtual meeting participants.

Meeting Live Poll for the 2022 Metabolomics Interest Group Meeting Theme: The organizers surveyed the attendees on the main challenge they face with their metabolomics data. From the 20 in-person attendees, 17 provided a response. Compound identification and informatics were among the topic two challenges indicated by the attendees. This provides an excellent opportunity for the interest group coordinators to focus and plan the 2022 workshop to address the needs of our members.



Featured Speakers: After speaking to a number of in-person attendees after the meeting, it was commonly stated that the talks delivered by the featured speakers were interesting, diverse in topics, informative, and very well received. The meeting poll scores for the meeting reflected the tone of these comments (Quality: 4.16/5; Topics: 4.28/5; Format: 4.17/5).

Lightening Talk Speakers: The three 5-min lightening talk speakers all performed a terrific job under the time constraints of the meeting format! Again, in-person attendees were impressed with the ability of the speakers to distill their projects down to just a few key points, produce graphics that were easy to grasp quickly and that were informative, and their ability to deliver an effective message in a short elevator-pitch type of presentation. Hoda Safari Yazd's talk with 8 votes from the in-person attendees was selected as the "People's Choice" Lightening Talk Award.