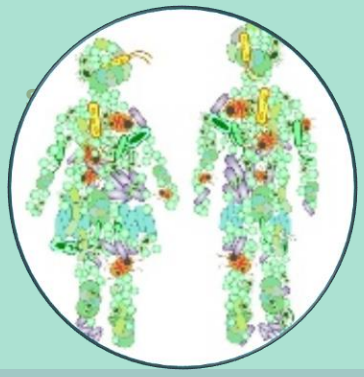

The Gut Microbiome: Markers of Human Health, Drug Efficacy and Xenobiotic Toxicity

June 25-26, 2018

625 First St.
Alexandria, VA

A workshop organized by the HESI Microbiome Committee

GOAL: To identify data gaps that can be addressed to help determine if alterations in the gut microbiome have an effect on human health

ABSTRACT: The gut microbiome is believed to play an important role in human health in areas as diverse as brain function and the immune system. Exploring host-microbiome interactions will provide a mechanistic understanding and enable new insights in human diseases (i.e., their diagnosis, prognosis and treatment) and new perceptions of xenobiotic efficacy and/or toxicity. This workshop will review the science and initiate discussions on multiple topics, including a) identification of biomarkers of toxicity for alterations in gut microbial function, b) if changes in the microbiome can affect efficacy of medicines and c) if exposure to xenobiotics can eventually result in a disease state through changes in the microbiome. Conclusions from this workshop will help determine where the data gaps are so that researchers can start answering these questions.

AIMS: (1) To discuss and review the current science on the gut microbiome and identify areas of interest regarding its role in human health; (2) To discuss our understanding on how xenobiotic toxicity affects the microbiome; (3) To understand if there are biomarkers of disease or organ damage due to alterations of microbiome structure and function, endogenous microbial metabolites and microbiota metabolism of exogenous compounds

PROGRAM OVERVIEW

Monday, June 25, 2018

Plenary

Session 1: Biotransformation – How does gut microbial metabolism and biotransformation affect xenobiotics and how do xenobiotics alter gut metabolism? Do the metabolites exert measurable biological activity compared to parent xenobiotic? Are there human or ADME studies in experimental animals on the bioavailability of the xenobiotic to intestinal microbiota?

Session 2: Biomarkers of adverse effects – Are there biomarkers that can be identified to determine adverse effects on the microbiome?

Session 3: Biomarkers of toxicity & disease – Do changes in the gut microbiome produce adverse effects that can impact the health of the host and result in the presence of biomarkers?

Light reception & Poster session

Tuesday, June 26, 2018

Session 4: Human Susceptibility – Does the gut microbiome play a part in individual responses?

Session 5: Animal Models – What are the variables that can alter the test animal microbiomes and can they be minimized to allow for the design and interpretation of studies that would be more applicable to the human condition?

Session 6: Breakout Groups

Workshop Schedule Overview

	MONDAY, JUNE 25	TUESDAY, JUNE 26	WEDNESDAY, JUNE 27
8:00 AM	**Welcome & Introduction** 8:00am – 8:15am	**Welcome & Recap Day 1** 8:30am – 8:40am	
	Plenary 8:15am – 9:00am		
9:00 AM	**Session 1** 9:00am – 9:40am		
	BREAK *9:40am – 10:00am*		
10:00 AM	**Session 1 (cont'd)** 10:00am – 11:20am	**Session 4** 8:40am – 10:40am	**Committee meeting** (closed) 8:30am – 1:30pm
11:00 AM		***BREAK*** *10:40am – 11:00am*	
	LUNCH *11:20am – 12:20pm*		
12:00 PM	**Session 2** 12:20pm – 3:00pm	**Session 5** 11:00am – 1:00pm	
1:00 PM		***BREAK/WORKING LUNCH*** *1:00pm – 1:30pm*	
2:00 PM		**Breakout Groups** 1:30pm – 3:30pm	
3:00 PM	***Break*** *3:00pm – 3:20pm*	***BREAK*** *3:30pm –3:50pm*	
	Session 3, Part 1 3:20pm – 5:20pm	**Report Back/Discussion** 3:50pm – 4:50pm	
4:00 PM		**Wrap-up/close** 4:50pm – 5:00pm	
5:00 PM	**Closing Remarks** 5:20pm – 5:30pm		
	Poster Session/Reception 5:30pm – 6:30pm		
6:00 PM			

DAY 1: MONDAY, JUNE 25

Welcome/Introduction

8:00am – 8:15am
Donna Mendrick, US FDA/NCTR

Plenary

8:15am – 9:00am
Drugging Gut Microbial Enzymes for the Treatment of Cardiometabolic Disease
Mark Brown, Cleveland Clinic

Session 1: Biotransformation

This session will evaluate three areas of gut microbiome mediated biotransformation of toxicants: 1) gut microbial metabolism and biotransformation of xenobiotics (including specific pathways, microbial metabolites and their metabolism in the host); 2) modification of chemical effects by the microbiome; and 3) how the microbiome affects xenobiotic toxicity. While there are numerous examples of the gut microbiome altering compounds, there have been no systematic efforts to examine how microbial enzymes present in the gut microbiota interact with a broad spectrum of chemicals. We will attempt to generalize this effort by providing linkages between classes of xenobiotics and enzymes classes. The focus will be on developing a better mechanistic understanding of how the gut microbiome influences how chemicals affect the host.

Moderated by: José Manautou (U Conn) and Vicki Sutherland (NIEHS/NTP)

9:00am – 9:40am
Overview of Biotransformation of Xenobiotics by Microbiota
Julia Cui, University of Washington

9:40am – 10:00 am
Break

10:00am – 10:40am
Gut Microbial Transformation – Endogenous and Exogenous Metabolites & Effect of Xenobiotics on Microbial Composition and Endogenous Functions
Gary Perdew, Penn State University

10:40am – 11:20am
Modification of Chemical Effects by Microbiome?
Andrew Patterson, Penn State University

11:20am – 12:20pm

Lunch

Session 2: Biomarkers of Adverse Effects

This session will evaluate three key issues to help identify biomarkers of adverse effects on the microbiome: 1) where to look for the biomarkers; 2) what level of specificity can be achieved (i.e., general biomarkers of adverse effects or ones that are specific for a given chemical); 3) what types of changes are most informative (e.g. changes in microbial populations, microbial products, or chemical metabolites). The source of sampling will be dependent on the microbiota of interest, but for the gastrointestinal microbiome, the most likely medium is fecal samples (though fecal samples may not be a reliable proxy for the dynamics of the microbiota at the mucosal surface). The

constant turnover of microorganisms within the GI tract will produce a baseline level of shedding of microbial populations, their DNA, and their protein components into the feces. Exposure to agents that adversely impact the GI microbiota may cause significant alterations in the abundance of microbial species (some species may be more susceptible than others), changes in the metabolites that are shed in the feces after the acute exposure, and/or a shift in baseline microflora with chronic exposure. Chemical-specific biomarkers could be used to identify alterations in specific pathways altered by exposure to exogenous agents. These biomarkers could potentially be detected within the feces or in other bodily fluids such as blood and urine.

Moderated by: Steve Foley (US FDA/NCTR) and Daniel Goldstein (Monsanto)

12:20pm – 1:00pm
What is an Adverse Effect?
Rodney Dietert, Cornell University

1:00pm – 1:40pm
Where to Look for Biomarkers?
Carrie Brodmerkel, Janssen

1:40pm – 2:20pm
Challenges in Determining Sensitive Biomarkers of Dysbiosis When Assessing the Impact of Antimicrobial Drug Residues in Food on the Human Intestinal Microbiome
Carl Cerniglia, US FDA-NCTR

2:20pm – 3:00pm
What are the Tools and Technologies Needed?
Joseph Petrosino, Baylor College of Medicine

3:00pm – 3:20pm
Break

Session 3: Biomarkers of Toxicity & Disease

Changes in the gut microbiome either through drug administration, alterations in diet, disease states, exposure to toxicants, etc. may produce an adverse effect and thereby have an impact on the health of the host. This can directly affect the GI tract or produce adverse effects in other organs or the system as a whole. In addition, organ injury to the host can disrupt symbiosis with resident microbes leading to potential changes in the microbiome. This session will focus on determining if changes in the microbiome due to xenobiotic-induced toxicities or disease resulting in host injury produces specific markers of such, and assessing if and how these "biomarkers" can be identified.

Moderated by: Sangeeta Khare (US FDA/NCTR) and Paul Carlson (US FDA/CBER)

3:20pm – 4:00pm
Toxicity and Environmental Pollutants
Kun Lu, University of North Carolina Chapel Hill

4:00pm – 4:40pm
Identification of Microbiome-based Biomarkers and Challenges Associated with their Application: Case Studies from Obesity, IBD, and Cancer
Emily Hollister, Diversigen

4:40pm – 5:20pm
The Microbiome and Hypertension
Elaine Richards Sumners, University of Florida

Day 1 Closing Remarks
5:20pm – 5:30pm
Donna Gulezian, Taconic Biosciences

Poster Session/Reception
5:30pm – 6:30pm

DAY 2: TUESDAY, JUNE 26

Opening Remarks
8:30am – 8:40am
Donna Gulezian, Taconic Biosciences

Session 4: Human Susceptibility
Susceptibility to adverse reactions (e.g., drugs and/or environmental agents) and drug efficacy is patient-specific suggesting multiple factors play a role. This is exhibited by patients that develop an idiosyncratic reaction to a drug yet can sometimes be placed back on the drug and tolerate it well. In general, about 70% of patients respond in an efficacious manner to individual drugs. Since the gut microbiome may be an important component in moderating effects of exogenous agents, it will be the focus of this session to determine if the gut microbiome plays a part in individual responses either through microbial metabolism of the compound, thus generating specific biomarkers or alteration of host uptake. Furthermore, as the drugs themselves may cause a change in the gut microbiome, it would necessitate following the flora in patients, during the course of their therapy, to determine if biomarkers of such alterations may lead to improved precision medicine.

Moderated by: Charlene McQueen (U Arizona) and Katherine Karberg (Monsanto)

8:40am – 9:20am
Health Insights from Microbiomes in the Context of Personal, Dense, Dynamic, Data Clouds
Nathan Price, Institute for Systems Biology

9:20am – 10:00am
Age – Early & Late Life
Eugene Chang, University of Chicago

10:00am – 10:40pm
Gender and the Gut Microbiome
Marijke Faas, University of Groningen

10:40am – 11:00am
Break

Session 5: Key Animal Models
There is currently an explosion of studies on the host microbiome that are based on experiments in mice. However, these experiments have also revealed that there are many variables that can alter the murine

microbiome, murine pathophysiology and biomarkers of organ injury, including diet, housing conditions, sex, stress, etc. Thus, guidance needs to be provided that can minimize these variables and allow for a more direct comparison across animal studies.

Moderated by: Howard Young (NIH/NCI) and Frank Burns (DuPont)

11:00am – 11:40am
Overview of Key Factors Known to Affect Composition of Laboratory Rodent Gut Microbiome
Aaron Ericsson, University of Missouri

11:40am – 12:20pm
Natural World Versus Laboratory World: Natural Gut Microbiota from Wild Mice Improve Host Fitness in Viral Infection and Carcinogenesis Models
Barbara Rehermann, NIH/NIDDK

12:20pm – 1:00pm
Investigating Interactions Between Chemicals and Microbiota in Zebrafish
Tamara Tal, US EPA

Break/Working Lunch

1:00pm – 1:30pm
Instructions and aims for breakout groups
Grab lunch and head to breakout groups

Working Lunch/Breakout Groups

1:30pm – 3:30pm

Break
3:30pm – 3:50pm

Breakout Groups Report-Back

3:50pm – 4:50pm

Workshop Wrap-up/Adjourn

4:50pm – 5:00pm
Vicki Sutherland, NIEHS/National Toxicology Program