PROGRAM BOOK

THE HUMAN MICROBIOME:

Emerging Themes at the Horizon of the 21st Century

August 16-18, 2017 • Natcher Conference Center, NIH

*The workshop organizers would like to thank Ms. Maria G. Paez Segala (amapollito17@gmail.com) for invoking the spirit of Giuseppe Arcimboldo (http://www.giuseppe-arcimboldo.org/) to create ‘microbiome family’ for the Emerging Themes workshop program.

TABLE OF CONTENTS

PURPOSE AND GOALS

This 2017 NIH-wide microbiome workshop was organized by a planning committee of the trans-NIH Microbiome Working Group (TMWG, https://commonfund.nih.gov/hmp/related_activities), which includes program staff from the 19 NIH Institutes, Centers, and Offices that support human microbiome research through their extramural portfolios. The TMWG is interested in taking stock of where the microbiome field stands after NIH's 10-year investment in the Human Microbiome Project (https://commonfund.nih.gov/hmp) and evaluating what is needed for this field to advance over the next decade. This meeting will strive to cover advances that reveal the specific ways in which the microbiota influences the physiology of the host, in both a healthy and a diseased state, and how the microbiota may be manipulated, at either the community, population, organismal, or molecular level, to maintain and/or improve the health of the host. The goal of this workshop is to seek input from a trans-disciplinary group of scientists to identify (1) knowledge gaps, (2) technical hurdles, (3) new approaches, and (4) research opportunities which will inform the development of novel prevention and treatment strategies based on host/microbiome interactions over the next 10 years. The workshop closes with an Joint Agency Panel that includes the seven other government agencies which support human microbiome research activities human microbiome research activities to discuss areas of common interest and possible collaboration.

ACKNOWLEDGMENTS

The trans-NIH Microbiome Working Group 2017 "Emerging Themes" workshop planning committee would like to acknowledge the generous support of the following NIH Institutes, Centers, and Offices for this workshop: NCI, NHLBI, NIDCR, NIDDK, NIEHS, NIGMS, NINR, NCCIH, OAR/OD, ODS/OD, and ORWH/OD. In particular, we would like to thank the Office of Strategic Coordination, fondly known as The Common Fund, for providing generous monetary support, but also for hosting the workshop website and always expressing encouragement and enthusiasm for this workshop's purpose and goals.

SOCIAL MEDIA

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PHOTOGRAPHY/VIDEOCASTING

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Presenters, please email the workshop organizers at **emerging_themes_workshop@nih.gov** if you do not want your talk webcast.

WORKSHOP URL

https://commonfund.nih.gov/hmp/meetings/emerging

Participants, monitor this website for updates to the program.

WORKSHOP EMAIL

etmicrobiome@gmail.com

Participants, use this email to submit questions for the daily Round Tables and the Joint Agency Panel.

AGENDA

This conference is being recorded and will be available via live webcast at:

The Human Microbiome: Emerging Themes at the Horizon of the 21st Century (Day 1)
https://videocast.nih.gov/live.asp?live=24940

The Human Microbiome: Emerging Themes at the Horizon of the 21st Century (Day 2)
https://videocast.nih.gov/live.asp?live=24944

The Human Microbiome: Emerging Themes at the Horizon of the 21st Century (Day 3)
https://videocast.nih.gov/live.asp?live=24948

Day One: Wednesday, August 16, 2017			
Theme of the Day: Overview and Approaches			
9:00 a.m.	**Opening Session I.**		
	9:00 a.m. – 9:15 a.m.	Call to Order and Charge to the Meeting Participants	*Moderator:* Lita Proctor National Human Genome Research Institute, NIH
	9:15 a.m. – 10:00 a.m.	Keynote I: What the Great Ape Microbiome Can Tell Us About the Human Microbiome	Howard Ochman University of Texas at Austin
10:05 a.m.	**Theme Session I. The NIH Human Microbiome Project: Catalyst for an Emerging Field**		
	Session Purpose: Reflect on the resources, outcomes, and legacy of the 10-year HMP program.		
	10:05 a.m. – 10:10 a.m.	Introduction to Session Purpose	*Moderator:* Lita Proctor National Human Genome Research Institute, NIH
	10:10 a.m. – 10:25 a.m.	The NIH Human Microbiome Project: Overview of HMP Program Goals and Accomplishments	Mary Ellen Perry Office of the Director, NIH
	10:25 a.m. – 10:40 a.m.	The Impact of the Microbiome of the Female Reproductive Tract on Health and Pregnancy	Gregory A. Buck Virginia Commonwealth University
	10:40 a.m. – 10:55 a.m.	Integrative Personal Omics Profiling During Periods of Environmental Stress	Michael P. Snyder Stanford University
	10:55 a.m. – 11:10 a.m.	Characterizing the Gut Microbial Ecosystem for Diagnosis and Therapy in Inflammatory Bowel Disease	Curtis Huttenhower T.H. Chan Harvard School of Public Health and Broad Institute

Day One: Wednesday, August 16, 2017			
	11:10 a.m. – 11:25 a.m.	Management and Integration of the iHMP Data	Owen R. White University of Maryland
	11:25 a.m. – 11:40 a.m.	Joint QA Session	
11:40 p.m.	11:40 a.m. – 1:00 p.m.	Lunch and Poster Session	
1:00 p.m.	**Theme Session II. State of the Art Microbiome Tools, Technologies, and Approaches #1: Beyond Sequencing**		
	Session Purpose: Highlight new tools/technologies for human microbiome research, what is appearing on the horizon, what other tools/technologies are needed, and what is needed to make progress in tool development for human microbiome research.		
	1:00 p.m. – 1:05 p.m.	Introduction to Session Purpose	*Moderator:* Lisa Chadwick National Institute of Environmental Health Sciences, NIH
	1:05 p.m. – 1:20 p.m.	Metagenotyping Reveals Cryptic Functional Variation in the Human Microbiome	Katherine S. Pollard University of California, San Francisco
	1:20 p.m. – 1:35 p.m.	Moving Microbiome Studies Toward Causality With Temporal and Spatial Visualizations	Rob Knight University of California, San Diego
	1:35 p.m. – 1:50 p.m.	The Need for Reproducible Global Chemical Analysis of the Microbiome by Mass Spectrometry	Pieter Dorrestein University of California, San Diego
	1:50 p.m. – 2:05 p.m.	Systems Biology and Model-Based Analysis of the Human Microbiome	Elhanan Borenstein University of Washington
	2:05 p.m. – 2:20 p.m.	Joint QA Session	
2:25 p.m.	**Theme Session III. State of the Art Microbiome Tools, Technologies, and Approaches #2: Alternate Models**		
	Session Purpose: Highlight new and novel animal and nonanimal models for human microbiome research, what other kinds of models are needed, and what is needed to make progress in model development.		
	2:25 p.m. – 2:30 p.m.	Introduction to Session Purpose	*Moderator:* Dwayne Lunsford National Institute of Dental and Craniofacial Research, NIH
	2:30 p.m. – 2:45 p.m.	Minibioreactor Arrays to Probe the Functions of Complex Microbial Communities	Robert A. Britton Baylor College of Medicine
	2:45 p.m. – 3:00 p.m.	The Drosophila Model for Gut Microbiome Research	Angela Douglas Cornell University

Day One: Wednesday, August 16, 2017			
	3:00 p.m. – 3:15 p.m.	Zebrafish as a Tractable Model for Host-Microbiome Interactions	John F. Rawls Duke University
	3:15 p.m. – 3:30 p.m.	Swine as a Preclinical Model for Human Gut Microbiome Research	Sharon M. Donovan University of Illinois
	3:30 p.m. – 3:45 p.m.	Spatiotemporal Metagenomics of the Mammalian Gut	Harris H. Wang Columbia University
	3:45 p.m. – 4:00 p.m.	Joint QA Session	
4:00 p.m.	4:00 p.m. – 4:30 p.m.	Break	
4:30 p.m.	**Theme Session IV. Issues for Microbiome Research Progress**		
	Session Purpose: Highlight general issues that impact human microbiome research progress and ideas on how to address them for future of the field.		
	4:30 p.m. – 4:35 p.m.	Introduction to Session Purpose	*Moderator:* Chris Lynch National Institute of Diabetes and Digestive and Kidney Diseases, NIH
	4:35 p.m. – 4:50 p.m.	Functional Roles of the Microbiome in Animal Model Experimentation	Thaddeus Stappenbeck Washington University, St. Louis
	4:50 p.m. – 5:05 p.m.	Ethical Issues in Human Microbiome Research: Beyond the Usual Suspects	Mildred Cho Stanford University
	5:05 p.m. – 5:20 p.m.	Joint QA Session	
5:25 p.m.	**Round Table Discussion I**		
	Moderator: Mike Reddy, National Institute for General Medical Sciences, NIH		
	5:25 p.m. – 5:55 p.m.	All Speakers From Day One	
5:55 p.m.	**Day One Ends**		

Day Two: Thursday, August 17, 2017			
Theme of the Day: Interactions of the Host-Microbiome System			
8:15 a.m.	**Opening Session II.**		
	Moderator: Bob Karp, National Institute of Diabetes and Digestive and Kidney Diseases, NIH		
	8:15 a.m. – 9:00 a.m.	Keynote II: The Gut Microbiota and Childhood Undernutrition: Looking at Human Development from a Microbial Perspective	Jeffrey I. Gordon Washington University, St. Louis
9:05 a.m.	**Theme Session V. Host-Microbiota Interactions**		
	Session Purpose: Highlight mechanistic or specific functional examples of host-microbe interactions, what is still not well understood about these interactions, and what is needed to make progress in understanding interactions.		
	9:05 a.m. – 9:10 a.m.	Introduction to Session Purpose	*Moderator:* Gabriela Riscuta National Cancer Institute, NIH
	9:10 a.m. – 9:25 a.m.	Gut Microbiota, Diet, Chronic Inflammation, and Metabolic Syndrome	Andrew Gewirtz Georgia State University
	9:25 a.m. – 9:40 a.m.	NLRP6: Current Challenges on Studying the Impact of the Microbiome on Host Responses	Dana Philpott University of Toronto
	9:40 a.m. – 9:55 a.m.	Antimicrobial Peptides Shape Intestinal Bacterial Niche Creation and Competition	Nita H. Salzman Medical College of Wisconsin
	9:55 a.m. – 10:10 a.m.	Microbes, Molecules, and Mucosal Immunity	Ramnik Xavier Harvard University
	10:10 a.m. – 10:25 a.m.	Joint QA Session	
10:25 a.m.	10:25 a.m. – 10:55 a.m.	Break	

Day Two: Thursday, August 17, 2017			
10:55 a.m.	**Theme Session VI. Microbe-Microbe Interactions within the Human Microbiome**		
	Session Purpose: Highlight concrete examples of microbe-microbe and interkingdom interactions in the microbiome and how these interactions affect/regulate human health and disease, what is still not understood about the role of microbe-microbe interactions in human health and disease, and what is needed to make progress in this area.		
	10:55 a.m. – 11:00 a.m.	Introduction to Session Purpose	*Moderator:* Roberto Flores National Cancer Institute, NIH
	11:00 a.m. – 11:15 a.m.	Understanding and Predicting the Impact of Antibiotic Therapy on the Developing Pediatric Microbiota and Resistome	Gautam Dantas Washington University, St. Louis
	11:15 a.m. – 11:30 a.m.	Bacteriome and Mycobiome Polymicrobial Interactions Define Health and Disease: A New Paradigm	Mahmoud Ghannoum Case Western Reserve University
	11:30 a.m. – 11:45 a.m.	Decoding Nutritional Interactions in Microbial Communities	Michiko E. Taga University of California, Berkeley
	11:45 a.m. – 12:00 p.m.	How Phages Create an Immune System: BAM Immunity and Transcytosis	Forest Rohwer San Diego State University
	12:00 p.m. – 12:15 p.m.	Joint QA Session	
12:15 p.m.	12:15 p.m. – 1:45 p.m.	Lunch and Poster Session	
1:45 p.m.	**Theme Session VII. The Intimate Relationship Between Diet and the Microbiome**		
	Session Purpose: Highlight current knowledge on the bidirectional influence of diet and dietary components on microbial and host metabolism and how the metabolites influence host physiology, what is still not understood about diet-microbe interactions in human health and disease, and what is needed to make progress in this area.		
	1:45 p.m. – 1:50 p.m.	Introduction to Session Purpose	*Moderator:* Cindy Davis Office of Dietary Supplements, NIH
	1:50 p.m. – 2:05 p.m.	Leaving Limbo: Stepping Back to Build a Strong Foundation of Mechanism and Stepping Forward to Dietary Interventions in Humans	Justin Sonnenburg Stanford University
	2:05 p.m. – 2:20 p.m.	Intestinal Epithelial Cell Receptors as Modulators of Host-Microbiota Communication	Andrew D. Patterson Pennsylvania State University

Day Two: Thursday, August 17, 2017			
	2:20 p.m. – 2:35 p.m.	Diet, the Gut Microbiome, and Its Metabolome as a Therapeutic Probe in IBD	Gary D. Wu University of Pennsylvania
	2:35 p.m. – 2:50 p.m.	How Gut Bacteria Eat Your Veggies: Molecular Details of Glycan Scavenging at the Cell Surface	Nicole Koropatkin University of Michigan
	2:50 p.m. – 3:05 p.m.	Testing Diet-Gut Microbiome Interactions: Use of Controlled Feeding Studies in Humans	Johanna W. Lampe Fred Hutchinson Cancer Research Center
	3:05 p.m. – 3:20 p.m.	Joint QA Session	
3:20 p.m.	3:20 p.m. – 3:50 p.m.	Break	
3:50 p.m.	**Theme Session VIII. Role of the Microbiome in Disease Initiation or Exacerbation: Moving Beyond Associations**		
	Session Purpose: Highlight concrete "cause and effect" mechanistic examples of the microbiome role in disease initiation or exacerbation, what is not yet understood about how the microbiome initiates or exacerbates disease, and what is needed to make progress in this area.		
	3:50 p.m. – 3:55 p.m.	Introduction to Session Purpose	*Moderator:* Lis Caler National Heart, Lung, and Blood Institute, NIH
	3:55 p.m. – 4:10 p.m.	Efforts to Understand Causation in Microbiota-Host Interaction: Two Examples	Andrew Goodman Yale University
	4:10 p.m. – 4:25 p.m.	Bile Acid-Microbiota Cross-Talk and Its Effects on Liver Cancer	Wei Jia University of Hawaii
	4:25 p.m. – 4:40 p.m.	Biofilms as a Risk Factor for Human Colon Cancer	Cynthia L. Sears Johns Hopkins University
	4:40 p.m. – 4:55 p.m.	Role of the Lung Microbiome in Respiratory Health and Disease	Gary B. Huffnagle University of Michigan
	4:55 p.m. – 5:10 p.m.	Joint QA Session	
5:15 p.m.	**Round Table Discussion II**		
	Moderator: Ryan Ranallo, National Institute of Allergy and Infectious Diseases, NIH		
	5:15 p.m. – 5:45 p.m.	Speakers From Day Two	
5:45 p.m.	**Day Two Ends**		

Day Three: Friday, August 18, 2017			
Theme of the Day: Microbiome Interventions for Maintaining Health and Treating Disease			
8:15 a.m.	**Opening Session III.**		
	Moderator: Ryan Ranallo, National Institute of Allergy and Infectious Diseases, NIH		
	8:15 a.m. – 9:00 a.m.	Keynote III: Microbiome Interventions: From Fecal Transplants to Synthetic Microbial Therapeutics	Eric Alm Massachusetts Institute of Technology
9:05 a.m.	**Theme Session IX. Translation of the Microbiome #1: Role of the Microbiome in Disease Prevention and Treatment**		
	Session Purpose: Highlight concrete examples of the role of the microbiome at the community, population, cellular, or molecular level in disease prevention and health maintenance; what is still not understood about the properties of the microbiome that can be exploited for disease prevention and health maintenance; and what is needed for progress in this area.		
	9:05 a.m. – 9:10 a.m.	Introduction to Session Purpose	*Moderator:* Padma Maruvada National Institute of Diabetes and Digestive and Kidney Diseases, NIH
	9:10 a.m. – 9:25 a.m.	Toward a Metagenomic Basis of Therapeutics	Peter J. Turnbaugh University of California, San Francisco
	9:25 a.m. – 9:40 a.m.	Gut Microbial Metabolites and Cancer Prevention	Scott J. Bultman The University of North Carolina at Chapel Hill
	9:40 a.m. – 9:55 a.m.	Microbiomes and Phenotypes: Impact, Restoration, and Transfer	Maria Gloria Dominguez-Bello New York University
	9:55 a.m. – 10:10 a.m.	Allogeneic Hematopoietic Stem Cell Transplantation: Clinical Outcomes, Intestinal Bacteria, and Potential Mechanisms	Robert Jenq The University of Texas MD Anderson Cancer Center
	10:10 a.m. – 10:25 a.m.	Joint QA Session	
10:25 a.m.	10:25 a.m. – 10:55 a.m.	Break	

Day Three: Friday, August 18, 2017			
10:55 a.m.	**Theme Session X. Translation of the Microbiome #2. Role of the Microbiome in Disease Prevention and Treatment**		
	Session Purpose: Highlight concrete examples of microbiome-based treatments for specific diseases, their outcomes, and new and novel microbiome-based interventions or treatments.		
	10:55 a.m. – 11:00 a.m.	Introduction to Session Purpose	*Moderator:* Dan Xi National Cancer Institute, NIH
	11:00 a.m. – 11:15 a.m.	Microbiota-Mediated Defense Against Antibiotic-Resistant Infections	Eric G. Pamer Memorial Sloan Kettering Cancer Center
	11:15 a.m. – 11:30 a.m.	Engineering Biological Computers for Human Health Applications	Timothy Lu Massachusetts Institute of Technology
	11:30 a.m. – 11:45 a.m.	Connecting the Gut Microbiome and Cancer Through Circadian Rhythms	Eugene B. Chang University of Chicago
	11:45 a.m. – 12:00 p.m.	Joint QA Session	
12:00 p.m.	12:00 p.m. – 1:30 p.m.	Lunch and Poster Session	
1:30 p.m.	**Joint Agency Panel**		
	Moderator: Lita Proctor, National Human Genome Research Institute, NIH		
	1:30 p.m. – 3:15 p.m.	*Agency Representatives:* Rajeev Agarwal Office of Research on Women's Health, NIH Paul Carlson U.S. Food and Drug Administration Stacy Carrington-Lawrence Office of AIDS Research, NIH Linda Chrisey Office of Naval Research, U.S. Department of Defense Zafar Iqbal U.S. Department of Veterans Affairs Scott Jackson National Institute of Standards and Technology Cliff McDonald Centers for Disease Control and Prevention Jack Okamuro U.S. Department of Agriculture	

Day Three: Friday, August 18, 2017		
		Jim Olds National Science Foundation Michael Sayre National Institute on Minority Health and Health Disparities, NIH
3:15 p.m.	**Workshop Wrap-Up**	
	3:15 p.m. – 3:30 p.m.	All workshop organizing members join stage
3:30 p.m.	**Day Three and Workshop End**	

SPEAKER ABSTRACTS

Keynote I: What the Great Ape Microbiome Can Tell Us about the Human Microbiome

Howard Ochman

Department of Integrative Biology, University of Texas at Austin

Despite the large body of work concerning the human microbiome and its role in human health, there is relatively little information about how the microbiome has evolved or the factors causing differentiation of microbial communities among species. Analysis of the gut microbiomes of great apes, including humans, revealed that the phylogeny based on microbiome compositions was congruent with the known relationships of the hosts. Investigations of the microbiomes of great apes have informed numerous features of the human microbiome, including the effects of social behavior, diet and disease state on microbiome contents, and the assortment of the gut microbial communities into enterotypes, which we have found to have preceded the split among great ape species. By comparing the gut microbiomes in a phylogenetic context, we reconstructed how the human microbiome has evolved accelerated rates and became depleted during great ape diversification. Furthermore, we show that certain bacterial lineages have co-diversified with great ape hosts over the past 15 million years. The next major challenge is to determine if these co-diversified lineages confer functional roles that are beneficial to certain host species and to specific subpopulations of humans.

The NIH Human Microbiome Project: Overview of HMP Program Goals and Accomplishments

Mary Ellen Perry

Office of Strategic Coordination, Office of the Director, NIH

From 2007 through 2016, the NIH provided almost $200M to the Human Microbiome Project (HMP). Inspired by advances in DNA sequencing technologies and bioinformatics tools, the HMP supported over 50 research teams to catalog and characterize the collection of microbes that live on and in us. The HMP set out to determine whether there was a core “healthy” microbiome and whether changes in the microbiome correlated with disease status, questions that could be answered for the first time using advanced bioinformatic approaches allowing identification and quantification of individual microbes from complex mixtures of DNA. HMP teams found that each healthy human tissue has a distinctive microbial community, and that, within each tissue, the specific microbes differ from person to person. They also found that the human microbiome is altered in multiple disorders from cancer to psoriasis, with the mixture of microbes being more diverse in some conditions and less diverse in others. More recently, HMP-supported investigators have been working to identify specific features of the microbiome that predict changes in health status through in-depth, longitudinal studies of hundreds of people who are pregnant, prediabetic or suffering from inflammatory bowel disease. Their new insights will be presented at this meeting and shared with the public through publications and on the Data Coordinating Center so that other researchers can continue to build on these discoveries. HMP-generated data and resources have helped to stimulate a rapidly growing field of research into the role of the microbiome in human health.

The Impact of the Microbiome of the Female Reproductive Tract on Health and Pregnancy

Gregory A. Buck

Center for the Study of Biological Complexity, Department of Microbiology and Immunology, Virginia Commonwealth University

The microbiome of the female reproductive tract is thought to have a major impact on women's reproductive health and well-being, including but not limited to health during pregnancy and its adverse outcomes including preterm birth and still birth. Bacterial vaginosis, with its still poorly defined etiology, has a point prevalence of up to 30%, and carries a higher risk for adverse pregnancy outcomes. Over 10% of pregancies terminate prematurely and some demographic groups (e.g., African Americans), experience a significantly higher incidence. The annual costs associated with preterm birth in the US exceed $25 billion. The Vaginal Microbiome Consortium at VCU and its collaborators, including the Global Alliance to Prevent Prematurity and Stillbirth, has collected cross-sectional samples from over 6,000 women, over 1,000 of whom were pregnant, and longitudinal samples from over 1,500 pregnant women. Samples include cervical, vaginal, buccal, rectal and skin swabs, and blood, plasma and urine, from pregnant women, placenta, cord and cord blood taken at birth, and buccal, meconium, skin and first stool samples from neonates. Approximately 10% of these women delivered prematurely.

We have analyzed selected panels of longitudinal samples from women who experienced term or preterm birth by taxonomic, metagenomic, metatranscriptomic, and cytokine profiling. Preliminary results confirm a uniquely complex microbiome in the female reproductive tract that shows racial biases, is altered during pregnancy, and is impacted by environmental and clinical factors. Multi-omic analyses of these data are identifying correlations between multi-omic profiles and clinical observations, and are suggestive of the impact of strain differences on pregancy outcome. The results are altering the traditional view of women's vaginal and reproductive health and promise earlier prediction of adverse reproductive events.

This work is supported by grants from the NIH Common Fund Human Microbiome Project program (1UH2/UH3AI08326 and 8U54HD080784 to G. Buck, K. Jefferson and J. Strauss). We thank all the members of the Vaginal Microbiome Consortium at VCU (vmc.vcu.edu) for their contributions to this project, and the Global Alliance for the Prevention of Prematurity and Stillbirth (gapps.org) for their participation and support.

Integrative Personal Omics Profiling During Periods of Environmental Stress

Michael P. Snyder

Department of Genetics and Center of Genomics and Personalized Medicine, Stanford University School of Medicine

Type 2 diabetes mellitus (T2D) is a significant health problem facing our nation, it's showed that early lifestyle or medical intervention in prediabetics can prevent conversion to T2D nearly by half, however, overall our ability to predict which individuals will develop T2D and when this will occur by which mechanism is strikingly inadequate. To better understand these factors for more effective early intervention, in particular to understand changes in response to various physiological stresses in prediabetes and whether those are associated with the risk to convert to T2D, we profiled 105 subjects

with more than 1000 longitudinal visits total that span over three years. Stresses we sampled included respiratory viral infection, antibiotics intakes and others that are linked to the development of diabetes previously. We measured millions of molecular analytes in host blood by multi-omics profiling, including on transcriptome, metabolome and proteome, and also tracked microbial taxonomic and gene changes of four body sites (nares, skin, tongue and gut) over those visits, to fully understand the complex molecular dynamics and regulations in the host-microbiome interactions. A subset of participants were then placed on a short-term high caloric diet, followed by additional multi-omic profiling. The dietary perturbation was associated with a wealth of biomolecular expression changes concomitant with weight gain and spanning multiple 'omes including the microbiome, and the omic response to weight gain differed between prediabetics and healthy controls. For another subset of participants who went through respiratory viral infections, their multi-omic profiling, including the microbiome, responded distinctly to different illness stages during the infection. Overall, the multi-omic profiles of individuals are unique compared to others regardless diet or illness perturbations. In total, these large-scale longitudinal data offer a novel and comprehensive view of the dysfunction in cellular networks associated with the progression to T2D and may offer new strategies for predicting and preventing the disease at a personalized level. In order to implement this integrative personalized omic approach into healthcare in a cost efficient and highly effective manner, future research is much needed in various areas, especially in improving the accuracy of omics measurement and bioinformatics prediction.

Characterizing the Gut Microbial Ecosystem for Diagnosis and Therapy in Inflammatory Bowel Disease

Curtis Huttenhower

T.H. Chan Harvard School of Public Health and Broad Institute

The inflammatory bowel diseases (IBD) are a model for complex microbiome-linked disease, and they include both Crohn's disease (CD) and ulcerative colitis (UC) and affect several million individuals worldwide. As part of the Integrative Human Microbiome Project, the IBDMDB (Inflamatory Bowel Disease Multi'omics Database) followed 100 CD patients, UC patients, and control subjects for one year each to generate integrated molecular profiles of host and microbial activity during disease. This includes 1,400 stool metagenomes, 700 metatranscriptomes, approximately 400 16S rRNA gene amplicon, RNA-seq, and epigenetic profiling of intestinal biopsies, and genetics and serology from all participants. Integration of microbial profiling with metabolomics has identified microbially-processed small molecules implicated in inflammation and disease severity. Likewise, combining metagenomics with metatranscriptomics has pinpointed microbes and pathways expressed uniquely within a subset of active disease patients. These data thus represent a substantial community resource for future multi'omics studies in IBD, and have also served to provide the first integrated molecular profile of immune activity and clinical response during disease progression.

Management and Integration of the iHMP Data

Owen R. White

Institute for Genome Sciences, University of Maryland School of Medicine

The Human Microbiome Project Data Coordination Center (HMP-DCC) played an important role in the success of the mission of the original HMP by providing a centralized location for researchers (both within and outside the HMP Research Network) to access HMP resources. The second phase of the HMP project known as the integrated Human Microbiome Project (iHMP), is focused on the interface between the microbiome and the host. The project has produced integrate multi-omic datasets from both the host and the microbiome. These datasets will allow the research community to gain insight into which properties of the host and microbiome, in combination, are key to human health and disease. As the types, size, and scope of the datasets produced under the iHMP have expanded, so has the need for effective organization and integration of the data as can be provided by the DCC. Previously the DCC web portal has met with great success and has been heavily used by the research community. All HMP phase 1 and iHMP primary data, derived data, protocols and other resources are now also available through our web resource. The web portal is a collection of data and associated services which provide users with multiple types of information and a diverse set of tools with which to do analysis. We will report on the data production, analysis systems, web portal capability and deposition into public archives in our presentation.

Metagenotyping Reveals Cryptic Functional Variation in the Human Microbiome

Katherine S. Pollard

Gladstone Institutes and University of California, San Francisco

Metagenotyping is the identification of microbial genetic variation from shotgun metagenomics data. Capturing genetic variants is important, because strains of the same species can differ significantly in gene content and gene sequence, which in turn affects the functional capabilities of microbial communities from one host to another. We developed high-throughput computational methods to identify single nucleotide variants and gene copy number variants within the specific microbial strains present in a shotgun metagenome, as well as phylogenetic models to test for associations between genetic variants and microbial or host traits. Using these methods, we tracked microbial transmissions from mothers to infants, discovered bacterial genes associated with colonization of the human gut, and quantified population genetic evidence for selection in prevalent gut microbes.

Moving Microbiome Studies Towards Causality With Temporal and Spatial Visualizations

Rob Knight

Departments of Pediatrics, Computer Science and Engineering, University of California, San Diego

Advances in DNA sequencing and metabolomics enable studies of hundreds to thousands of samples. Understanding these highly multivariate datasets poses considerable challenges due to the massive scale of the data and to features such as sparsity and compositionality that complicate interpretation. In moving from observational studies to identifying causal linkages, integration of multi-omics data in spatially and/or temporally resolved study designs provides insight that cannot be gained otherwise. In this talk, I demonstrate these principles with vignettes showing the utility of these techniques in interpreting the developing infant microbiome, the human skin microbiome, inflammatory bowel disease, a mouse model of cardiovascular disease, and the cystic fibrosis lung. Highlighting the repositories Qiita (http://qiita.ucsd.edu/) and GNPS (http://gnps.ucsd.edu/), the largest repositories of publicly available annotated microbiome and metabolome data respectively, I present a vision for deploying these techniqes broadly across studies of both human and model animal microbiomes to obtain fundamentally new ways of understanding host-microbiome interactions.

The Need for Reproducible Global Chemical Analysis of The Microbiome by Mass Spectrometry

Pieter Dorrestein

Departments of Pharmacology and Pediatrics, University of California, San Diego

Mass Spectrometry is starting to play a critical role in the elucidating the functional role of the microbiome and in our understanding how chemical environments drive niche colonization. In the past fifteen years, the cost of mass spectrometry has come down by two orders of magnitude per volume of data that is collected (https://www.nature.com/articles/s41570-017-0054). As the sensitivity of instrumentation increases by an order of magnitude, the number of unknowns doubles. One of the key limitations of untargeted mass spectrometry is the lack of data analysis reproducibility. If the same data is provided to different people, we have different outcomes. The second limitation is our ability to annotate molecules that can be observed. Currently in untargeted metabolomics, on average, only 2% of the data that is collected can be annotated, and there are very few mass spectral references for microbial molecules. To begin addressing some of these shortcomings, we launched a global data driven knowledge sharing and analysis infrastructure called global natural product social molecular networking or GNPS (http://www.nature.com/nbt/journal/v34/n8/full/nbt.3597.html). The GNPS community now counts 26,000 users from 136 countries. One of the key features of GNPS is that is allows public sharing of raw data. This is critical for scientific reproducibility and argue that only sharing of tables with m/z, features and annotations is not appropriate. When the raw data is not available, the results tables cannot be updated with the most advanced analysis tools and knowledge of the future. This is important as new algorithms are rapidly advancing. In this 15 min discussion talk I will discuss (1) the continued need for the development reproducible data workflows. (2) The need for curated reference data sets. (3) Improve the reference libraries for microbial molecules – in silico methods play a key role in this. (4) The need for microbiome specific workflows – some may replace sequencing in certain circumstances if done correctly perhaps one day realizing near real time analysis of the microbiome. This will only be possible with the informatics platform running in the background.

Systems Biology and Model-Based Analysis of the Human Microbiome

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University of Washington and Santa Fe Institute

The human microbiome – the diverse ensemble of microorganisms that populate the human body – represents a vastly complex ecosystem that is tightly linked to our health. Multiple molecular assays now enable high-throughput profiling of this system, providing large-scale and comprehensive characterization of its ecology, functional capacity, and metabolic activity. To date, however, analyses of such multi-omic data typically focus on statistical associations, often ignoring extensive prior knowledge of the mechanisms, dependencies, and regularities linking these various facets of the microbiome. In this talk, I will highlight the pressing need for the development of predictive systems-level models of the microbiome and of model-based methods for integrating and analyzing microbiome multi-omic data. I will further introduce several novel computational frameworks for linking taxonomic, genomic, metagenomic, and metabolomic information about the microbiome. Combined, such frameworks lead to an improved comprehensive, multi-scale, and mechanistic understanding of the microbiome in health and disease, informing efforts for personalized microbiome-based therapy.

Mini-Bioreactor Arrays to Probe the Functions of Complex Microbial Communities

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Over the past decade there has been a concerted effort to catalog the microbes that are associated with the human body. These studies have demonstrated the enormous complexity of these communities and have shown clear associations with health and disease. However, our understanding of the functional contributions of microbial communities and the underlying mechanisms is a critical knowledge gap that exists in our field. To address this gap, we have created minibioreactor arrays (MBRAs) to facilitate the cultivation and functional analysis of complex microbial communities. Seeded with human fecal samples, MBRAs support the growth of diverse communities that establish functions associated with intestinal communities including resistance to pathogen invasion and transformation of dietary metabolites. Individual fecal samples exhibit unique functions, demonstrating that communities established from different individuals retain functional capabilities. Antibiotic treatment of MBRA communities alters their functions including allowing for the invasion of the pathogen *Clostridium difficile*. The establishment of technologies that allow for the cultivation of complex microbial communities that not only retain key functions but also provide opportunities for the manipulation of community function will be critical for elucidating mechanisms by which the microbiota impacts human health.

The Drosophila Model for Gut Microbiome Research

Angela Douglas

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There is now strong evidence that the gut microbiome plays a central role in the metabolic health of Drosophila fruit flies, protecting the fly against hyperlipidemia and hyperglycemia, as well as contributing to the nitrogen nutrition and B vitamin requirements of the insect. The Drosophila microbiome is very tractable to study the fundamental processes underlying the impact of the gut microbiome on human metabolic health and disease. In particular, the gut microbiota is of low diversity and mostly culturable, with key bacterial taxa amenable to genetic manipulation. It is cheap and technically straightforward to generate and maintain germ-free Drosophila; and to construct flies with a standardized microbiota for experimental study. The suitability of Drosophila for large and complex experimental designs is illustrated by GWAS experiments enabling identification of candidate host and microbial genes determining microbial colonization and microbiota-mediated effects on metabolism. Interpreting results from these experiments is facilitated by a suite of genetic and metabolic approaches, including metabolic modeling, to interrogate the underlying mechanisms. These studies reveal the central role of microbial fermentation products in shaping host metabolic function, mediated at least in part through microbial promotion of mobilization of lipid reserves. They also highlight interactions between the impacts of the microbiota on metabolism and the function of both the immune system and nervous system, providing the opportunity for integrated analysis of microbiome impacts on metabolism, protection against pathogens, and behavior.

Zebrafish as a Tractable Model for Host-Microbiome Interactions

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The field of microbiome science has revealed remarkable diversity of microbial life associated with humans and other animals, and has uncovered associations between specific microbiome configurations and human health. By comparison, we understand relatively little of the molecular and cellular mechanisms utilized by specific microbial and host cells to mediate these host-microbiome interactions. These gaps in knowledge can be addressed using experimental systems that permit high-throughput identification of host and microbial mechanisms along a range of temporal and spatial scales. The zebrafish has emerged as a powerful vertebrate model system for addressing these challenges. The small size and optical transparency of the zebrafish facilitate high-resolution in vivo imaging as well as high-throughput gnotobiotic manipulations that complement the technical and biological limitations of other model systems. Extensive anatomic, physiologic, and genomic homologies between zebrafish and mammals permit translation of insights gained in zebrafish into advances in human medicine. Studies using the zebrafish have revealed novel molecular, nutritional, and ecological processes underlying host-microbiome interactions. For example, we recently used the zebrafish to discover a critical and evolutionarily conserved role for the host transcription factor Hepatocyte nuclear factor 4 alpha (HNF4A) in maintaining intestinal homeostasis in response to the microbiome. We also recently developed a method for genetic analysis in bacteria that are otherwise intractable to molecular genetic manipulation, and demonstrated its utility in a representative Firmicutes bacterium from the zebrafish intestine. Future goals for the zebrafish model include building new tools for visualizing and measuring

microbial and host physiologies in live animals with improved spatial and temporal resolution, advancing gnotobiotic zebrafish husbandry methods to empower high-throughput and long-term studies, and expanding and improving the available zebrafish models of human microbiome-related diseases.

Swine as a Preclinical Model for Human Gut Microbiome Research

Sharon M. Donovan

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Defining the mechanistic underpinnings whereby the intestinal microbiota influences human health and disease has been hampered in part by variation in genetics, physiology and microbiota between humans and rodent models. Swine are an important agricultural species as well as excellent models for human physiology, nutrition, pathologies and infectious diseases. For that reason, research using swine is said to serve dual purpose and dual benefit. Both species are omnivorous, the size and composition of the porcine genome are comparable to those of humans and the swine immune system is 80% homologous to the human. Additionally, organ systems generally share common functional features between the species, particularly the gastrointestinal and neural systems. The swine gut microbial community is influenced by age, sex and genetics and markedly influences animal health and growth performance. In adult swine, the gut microbiota 16S rRNA sequences are similar to humans at the level of the pyla and major taxa. Additionally, deep metagenome sequencing of swine fecal DNA identified 7.7 million non-redundant genes representing 719 metagenomic species. Importantly, 96% of the functional pathways in the human metagenome catalogue are present in the pig catalogue, supporting the potential use of pigs for biomedical research. Our lab has extensively utilized the piglet as a model for neonatal human gut, immune and cognitive development and nutritional modulation of gut microbiome composition and metagenome. However, the microbiome of the developing piglet is lactobacillus-predominant, with a low abundance of bifidobacteria. To overcome this limitation, germ-free and gnotobiotic piglets colonized with bifidobacteria or human microbiota have been established and are providing a malleable model system in which to probe microbiome-modulation of neonatal development.

Spatiotemporal Metagenomics of the Mammalian Gut

Harris H. Wang

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A key knowledge gap in the gut microbiome is the detailed delineation of the spatial and temporal organization of microbiota at a single-cell level. A variety of environmental and host factors such as diet, drugs, genetics may influence the microbial spatiotemporal distribution to maintain healthy homeostatic states or cause dysbiotic pathologies. We describe new metagenomic approaches to map the spatial biogeography of the gut microbiome at a micron-scale resolution and temporal functional metagenomic selection in the mammalian gut. Understanding the natural spatiotemporal associations between microbiota, and with the host, will enhance the mechanistic dissection mediating their interactions at the community, cellular, and genetic level. Furthermore, disruptions to the natural biogeography could serve as a new clinical biomarker for microbial dysbiosis beyond species composition or abundance signatures. These understandings could lead to development of complex synthetic gut communities that recapitulate the various physiological contributions of a natural microbiota to host gut health and function.

Functional Roles of the Microbiome in Animal Model Experimentation

Thaddeus Stappenbeck

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Mammals are defined by their metagenome, a combination of host and microbiome genes. It is increasingly clear that the metagenome plays a role in a wide range of human diseases. When modeling features of human diseases in animal models such as mice, it is important to design experiments that take this principle into account. Implementation of strategies to account for the metagenome and develop methods to accurately communicate this information is critical to our work as a community in decipher in the pathogenesis of a variety of disease states. I will highlight a disease state, acute influenza infection that in mouse models is well known to be influenced by the microbiome component of the metagenome. We found that there are specific microbes and microbial products that impact the outcome of this pathogen on the host. This work highlights an example whereby attention to the metagenome in mouse models can lead to new insights into disease pathogenesis.

Ethical Issues in Human Microbiome Research: Beyond the Usual Suspects

Mildred Cho

Center for Biomedical Ethics and Professor, Departments of Pediatrics and Medicine, Stanford University

Study of the human microbiome is upending fundamental ways of thinking about human health and disease. In addition, products meant to manipulate the human microbiome often defy categories on which our regulatory system is based. For example, how should clinicians, patients, product developers and regulators think about and proceed with the use of fecal microbiota transplants for serious emergent conditions such as *Clostridium difficile* infections, or for less urgent conditions such as obesity? At the same time, human microbiome research is being conducted during what could be a radical restructuring of science, enabled by broad access to information and materials, with broad participation of patients, customers and the interested public. This “citizen scientist,” crowd sourcing and crowd funding movements, in combination with large scale efforts such as the All of Us / Precision Medicine Initiative, raise ethical issues that could pose challenges to the ability to the progress and translation of human microbiome research.

Keynote II: The Gut Microbiota and Childhood Undernutrition: Looking at Human Development from a Microbial Perspective

Jeffrey I. Gordon

Center for Genome Sciences and Systems Biology, and Center for Gut Microbiome and Nutrition Research, Washington University School of Medicine, St. Louis

Human postnatal development is typically viewed from the perspective of our “human” organs. As we come to appreciate how our microbial communities are assembled following birth, there is an opportunity to determine how this microbial facet of our developmental biology is related to healthy growth as well as to the risk for and manifestations of disorders that produce abnormal growth. We are testing the hypothesis that perturbations in the normal development of the gut microbiota are causally

related to childhood undernutrition, a devastating global health problem whose long-term sequelae, including stunting, neurodevelopmental abnormalities and immune dysfunction, remain largely refractory to current therapeutic interventions. The journey to preclinical proof-of-concept, and the path forward to clinical proof-of-concept emphasize the opportunities and challenges for developing microbiota-directed therapeutics, including products positioned at the intersection of food and medicine.

One critical gap: Define the metabolic underpinnings of microbial succession.

Gut Microbiota, Diet, Chronic Inflammation, and Metabolic Syndrome

Andrew Gewirtz

Institute for Biomedical Sciences, Georgia State University

The intestinal tract is inhabited by a large diverse community of bacteria collectively referred to as the gut microbiota. Alterations in gut microbiota composition are associated with a variety of disease states including obesity, diabetes, and inflammatory bowel disease (IBD). Transplant of microbiota from diseased persons (or mice) to germfree mice transfers some aspects of disease phenotype, indicating that altered microbiota plays a role in disease manifestation. There are myriad potential mechanisms by which alterations in gut microbiota might promote disease including increasing energy harvest, production of toxic metabolites, and molecular mimicry of host proteins. However, our research indicates that an overarching mechanism by which an aberrant microbiota negatively impacts health is by driving chronic inflammation. More specifically, we hypothesize that the histopathologically-evident gut inflammation that defines IBD is a severe but relatively rare outcome of an altered host-microbiota relationship while a much more common consequence of such disturbances is “low-grade” inflammation, characterized by elevated proinflammatory gene expression, that associates with, and may promote, metabolic syndrome. In this context, a variety of chronic inflammatory diseases may stem from inability of the mucosal immune system to properly manage a stable healthy relationship with the gut microbiota. Diet in general and food additives in particular, play an essential role in shaping microbiota composition and its functional activities. Thus, such additives can influence development of metabolic diseases.

NLRP6: Current Challenges on Studying the Impact of the Microbiome on Host Responses

Dana Philpott

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As we have come to appreciate the influence of gut bacteria on various diseases, we are presented with new challenges in determining how experimental results and the reproducibility of in vivo animal models are impacted by the combined effects of the genetics of the host and the host-associated microorganisms, from bacteria, viruses, fungi and beyond (i.e., the metagenome). The use of littermate-controlled animals from heterozygous breeding pairs is the gold-standard for normalizing genetic and environmental variability. The NOD-like receptor, NLRP6, was previously shown to strongly influence gut microbial communities and impact intestinal inflammation, however, none of these studies were obtained using littermate animals, opening up the possibility that the pro-colitogenic microbiota

phenotype associated with knockout mice was stochastically acquired and genotype-independent. We decided to revisit the role of NLRP6 by analyzing the microbiota in littermate animals. WT and Nlrp6-/- male and female littermate mice from a heterozygote cross, either co-caged or individually caged after weaning showed no significant differences in their microbiomes. However, our results confirm a previously reported sex-biased microbial community structure, which was evident in both WT and Nlrp6-/- mice. Furthermore, we surprisingly observed that while WT and Nlrp6-/- males displayed similar sensitivity to DSS-induced colitis, female Nlrp6-/- mice were more susceptible than female WT animals. Therefore, our results clarify the role of NLRP6 in microbiota and colitis control, and highlight the current challenge in microbiome research and studying its effect on host responses. Indeed, researchers need to analyze littermate mice as well as account for sex differences for these studies to be meaningful.

Antimicrobial Peptides Shape Intestinal Bacterial Niche Creation and Competition

Nita H. Salzman

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Antimicrobial peptides (AMPs) are among the most ubiquitous, conserved and evolutionarily ancient mediators of host-microbe interaction, found throughout the plant and animal kingdoms. While there has been considerable attention to the importance of AMPs in host defense against pathogens, their essential homeostatic role has recently become evident more recently. We and others have shown that mammalian intestinal mucosal AMPs are essential for both defending against enteric pathogens and mediating homeostasis with the intestinal microbiota. Conversely, bacteria have developed AMP resistance mechanisms to allow their survival in the intestinal milieu, a trait that facilitates both commensal colonization and pathogenic invasion. Composition of the intestinal antimicrobial environment is not limited to host-derived AMPs. Intestinal microbes also produce and secrete antimicrobial factors. Most recently, we have investigated the role of bacterial AMPs, bacteriocins, in intestinal colonization by *Enterococcus faecalis* (EF), an intestinal commensal and opportunistic pathogen of humans. Bacteriocins are plasmid encoded AMPs that facilitate intra-genus communication and niche-competition. Using a mouse model of stable enterococcal GI tract colonization, we found that enterococcal bacteriocin production resulted in enhanced colonization and niche-competition without profound disruption of the gut microbiome, suggesting the potential utility of GI niche-targeting for manipulation of the intestinal microbiota. Conversely, differential host response to EF bacteriocin production suggests that bacteriocins may have a role in microbe-host signaling and communication.

Our ability to manipulate the intestinal microbiome to benefit human health and to eliminate pathogenic colonization or invasion requires a more sophisticated understanding of microbe-microbe and microbe-host interaction within the GI tract. Incomplete understanding of commensal physiology and interspecies communication are limiting our ability to make optimal sense of the massive multi-omics data sets generated from animal and human microbiome studies. Detailed understanding of the biology of specific commensal populations that comprise the microbiota will enhance sequence databases through improved gene annotation, and allow the focused manipulation of microbial populations to benefit health while reducing collateral damage to the host.

Microbes, Molecules, and Mucosal Immunity

Ramnik Xavier

Harvard Medical School and Broad Institute, Harvard University

Taxonomic and functional changes to the composition of the gut microbiome have been implicated in multiple human diseases. Recent microbiome genome-wide association studies reveal that variants in many human genes involved in immunity and gut architecture are associated with an altered composition of the gut microbiome. Although many factors can affect the microbial organisms residing in the gut, a number of recent findings support the hypothesis that certain host genetic variants predispose an individual towards microbiome dysbiosis. Presentation will focus on how the microbiota drives intestinal disease based on host genetics, disruption of microbial community architecture and pathways that disrupt mucosal homeostasis.

Understanding and Predicting the Impact of Antibiotic Therapy on the Developing Pediatric Microbiota and Resistome

Gautam Dantas

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Early life is a critical developmental window for the gut microbiota, and perturbations that occur during this period are likely to have long lasting effects on host physiology and health. It is thus important to understand and predict the specific effects of perturbations, such as antibiotic treatment, on this dynamic and developing microbial ecosystem. We are using a multipronged metagenomic and culture-based approach to characterize the acute and persistent effects of antibiotic treatment on the developing infant gut microbiota. We found that during the first few months of life, the preterm infant gut microbiota is significantly lower in diversity than the microbiota of age-matched term infants, and is dominated by multi-drug resistant facultative anaerobes. Functional metagenomic interrogation revealed that the preterm infant gut microbiota encodes an extensive and diverse resistome that is enriched in a drug-specific manner following antibiotic treatment. We also observed that while most antibiotics are associated with significant decreases in species richness in the preterm microbiota, vancomycin and gentamicin have variable but predictable species richness responses. Our ongoing tandem sequencing and culture-based analysis of samples collected following discharge from the neonatal intensive care unit indicate that while overall phylogenetic composition of the preterm infant gut microbiota recovers by 20 months of age, these infants may harbor high-risk, multidrug resistant Enterobacteriaceae strains which are enriched for during hospitalization. Finally, we have used machine-learning approaches to accurately predict infant microbiome responses to specific antibiotics based on key taxonomic and functional microbiome features. Such predictive algorithms could enable future microbiome-based personalized medicine approaches to tailor antibiotic treatments to treat infections while reducing collateral microbiota damage. However, a key knowledge gap that currently hampers our ability to achieve this goal is a quantitative understanding of the level of resolution (e.g., family, species, gene, nucleotide) required to appropriately inform clinically-actionable microbiome-based predictions. Determining the ideal molecular resolution required for predicting various phenotypic or clinical outcomes has clear technological and cost considerations (e.g., the need for deep shotgun metagenomic sequencing versus PCR of a specific informative locus). There is also the immense basic science value in bettering our understanding of phenotype-genotype relationships at different molecular resolutions.

Experimental and computational methods to address this “predictive microbiome resolution” gap will accelerate translation of existing predictive models and guide development of future therapeutics and diagnostics.

Bacteriome and Mycobiome Polymicrobial Interactions Defines Health and Disease: A New Paradigm

Mahmoud Ghannoum

Case Western Reserve University and University Hospital Cleveland Medical Center

Recent studies revealed that microbial communities (bacteriome and mycobiome) have adopted inter-kingdom cooperative evolutionary strategies that culminate in biofilm formation. In microbial dysbiosis, biofilms are beneficial to both bacterial and fungal communities but detrimental to the host. This inter-kingdom interaction is best exemplified in Crohn's disease (CD). We used Ion Torrent sequencing to characterize the gut bacterial microbiota (bacteriome) and fungal community (mycobiome) in patients with CD and their non-diseased first-degree relatives (NCDR) in familial clusters and in healthy individuals from families living in the same area (non-CD unrelated, NCDU). Principal components analysis, diversity, and abundance analyses were conducted and CD-associated inter- and intra-kingdom microbial correlations determined. Significant microbial interactions were identified and validated using single- and mixed-species biofilms. CD and NCDR groups clustered together in the mycobiome, but not in bacteriome. Microbiota of familial (CD, NCDR) samples were distinct from that of non-familial (NCDU) samples. Abundance of Serratia marcescens (SM), Escherichia coli (EC) was elevated in CD patients, while that of beneficial bacteria was decreased. Abundance of the fungus Candida tropicalis (CT) was significantly higher in CD compared to NCDR ($P = 0.003$), and positively correlated with levels of anti–Saccharomyces cerevisiae antibody (ASCA). Abundance of CT was positively correlated with SM and EC, suggesting these organisms interact in the gut. The mass and thickness of Triple species (CT+SM+EC) biofilm were significantly higher than single and double species biofilm. CT biofilms comprised of blastospores, while double and triple species biofilms were enriched in hyphae. SM used fimbriae to co-aggregate or attach with CT/EC, while EC closely apposed with CT. Specific inter-kingdom microbial interactions may be key determinants in CD. The ability fungi to form inter-kingdom biofilms with bacterial species emphasize, not only their paramount importance, but also the complexity of studying whole microbial communities, and their interspecies interactions. Investigations into mechanisms underlying these polymicrobial interactions are critical, warranted, and will lead to novel translational approaches that will impact chronic diseases.

Decoding Nutritional Interactions in Microbial Communities

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Nutritional interactions among microbes are major drivers of microbial community structure and metabolism. The majority of nutritional interactions in microbes are poorly understood, and methods to predict interactions based on sequence analysis are limited. A critical challenge in the effort to gain a deeper understanding of microbiomes is to make better use of the increasingly abundant (meta)genome sequencing data to predict nutritional interactions, i.e., to "decode" microbial interactions. Corrinoid (vitamin B12-like) cofactors are shared among bacteria: corrinoids are required by an estimated 80% of bacteria, yet they are produced by less than 40%. In the human gut, corrinoids are essential cofactors for diverse metabolic processes including methionine synthesis, deoxynucleotide synthesis, and the catabolism of various carbon sources that are present in the gut. Because corrinoids play critical roles in bacterial metabolism but half of bacteria do not synthesize corrinoids, understanding how corrinoids are shared among bacteria is necessary to achieve a more complete understanding of bacterial metabolism and community structure. Using genome analysis to predict corrinoid sharing is further complicated by the fact that corrinoids produced by different microbes have variations in their structure, and these structural variants are not functionally equivalent for corrinoid-dependent enzymes. We are investigating corrinoid biosynthesis pathways and the requirements for particular corrinoid structures in an effort to understand and predict corrinoid-based metabolism in microbial communities. By identifying new genes and characterizing protein sequence and function, we have begun to improve genomic predictions of corrinoid biosynthesis and corrinoid requirements. A greater understanding of corrinoid metabolism and structural specificity may lead to improved strategies for manipulating the metabolism or composition of microbiomes.

How Phage Create an Immune System: BAM Immunity and Transcytosis

Forest Rohwer

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Viruses, and particularly phage that infect bacteria, are the most abundance and diversity life forms on the planet. Given their success throughout the biosphere, it is expected that phage are essential members of the animal and plant holobionts. We have shown that phage form a bacterial selective, adaptive immune system that helps protect the mucosal surfaces of animals and establish the microbiome. Additionally, phage are actively transported across epithelial layers and may provide a systemic protection against bacteria. These two findings strongly suggest that phage formed the first acquired immune system and they remain important in extant animal immunology. The biggest knowledge gap in my field is the overly cell-centric nature of most researchers, editors and funders.

Leaving Limbo: Stepping Back to Build a Strong Foundation of Mechanism and Stepping Forward to Dietary Interventions in Humans

Justin Sonnenburg

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The trillions of microbes that live within the gut of each human represent a critical, yet dynamic component of our biology. The links between our gut microbiome and our health, combined with the malleability of this community, suggests that if we learn the rules for how to manipulate our gut microbes, we may be able to treat and prevent disease. Diet has emerged as one of the most powerful levers available to shape the composition and functionality of the gut microbiome. However, a primary challenge is to understand how to use diet to provide desired and predictable outcomes in the face of tremendous complexity and individuality of the gut community. The Sonnenburg lab is currently focused on understanding basic principles that govern diet-gut microbiome dynamics, and how interactions between nutrients and microbes within the gut can cascade into physiological changes to human biology. To pursue these aims, we apply systems approaches and use genetic tools for the model mouse host and microbes to gain mechanistic insight into emergent properties of the host-microbial super-organism. We are currently working to fill a critical gap in enabling the manipulation and tracking of single strains and cells within complex communities. We also use a variety of tools and technologies to manipulate and measure microbiota and host biology in humans undergoing dietary intervention. Development of humans as an experimental model to study the microbiome-immune-metabolism axis, and how this axis can be manipulated by diet for improved human health remains a major challenge in the field.

Intestinal Epithelial Cell Receptors as Modulators of Host-Microbiota Communication

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A complex network of host receptors and microbiota within the gastrointestinal tract work in concert to process and absorb dietary nutrients, detoxify xenobiotics, and establish a homeostatic system that regulates metabolism and inflammation. Emerging evidence suggests ligand-activated transcription factors of the nuclear receptor superfamily and the basic helix-loop-helix/per-arnt-sim (PAS) family not only receive and process chemical signals derived from microbial-dependent metabolic activity, but also transmit these signals to distant organs, including the liver. For example, small intestine signaling of the farnesoid X receptor (FXR), an essential regulator of bile acid, lipid, and glucose metabolism, is modulated through gut microbiome-dependent metabolism of bile acid metabolites produced in the liver. Additionally, studies of the aryl hydrocarbon receptor (AHR), a xenobiotic sensor, have revealed microbial metabolites derived from dietary nutrients including tryptophan as critical regulators of both intestinal and hepatic inflammation. Dissection of the host-metabolite-microbiome interaction was facilitated by use of transgenic mouse models, host and microbiome sequencing, and mass spectrometry- and NMR-based metabolomics. Identification and characterization of microbial metabolites and their relationship with host receptors will provide new avenues for studying host-microbiota communication networks and identifying new therapeutics to modulate this interaction in human disease.

Gap: Understanding of the full repertoire of metabolites produced and/or modified by the microbiota is limited. Identification of microbial products by mass spectrometry- and NMR-based analytical chemistry and functional characterization—for example, ligand binding assays—could illuminate the host-microbiome chemical dark matter.

Diet, the Gut Microbiome, and its Metabolome as a Therapeutic Probe in IBD

Gary D. Wu

University of Pennsylvania School of Medicine'

Despite its importance in maintaining the health of the host, growing evidence suggests the gut microbiota may also be an important factor in the pathogenesis of various diseases, a number of which have shown a rapid increase in incidence over the past few decades. In some of these diseases, such as IBD, the microbiota is “dysbiotic” with an altered community structure and decrease in diversity. If the dysbiotic microbiota plays a role in disease pathogenesis, interventions that modify its composition might be a strategy to treat certain disease processes. There is epidemiologic data associating diet with the development of inflammatory bowel disease (IBD) as well as evidence that diet can influence both the form and function of the microbiome in a manner that impacts upon the development of intestinal inflammation. Based on this evidence, studies are now underway to examine the effect of defined formula diets (DFDs), an effective therapeutic modality in Crohn’s disease, on both the gut microbiome and its metabolome as a therapeutic probe with the hope of better defining the “healthy” diet in patients with IBD. Data will be presented from two human intervention studies, Pediatric Longitudinal Study of Elemental Diet and Stool Microbiota Composition (PLEASE) as well as Food And Resulting Microbial Metabolites (FARMM) designed with the intent of developing a systematic and integrated approach to alter the environment of the gut via diet and the gut microbiota to develop non-immunosuppressive modalities to treat IBD by engineering the environment of the gut.

How Gut Bacteria Eat Your Veggies: Molecular Details of Glycan Scavenging at the Cell Surface

Nicole Koropatkin

Department of Microbiology and Immunology, University of Michigan

Mammalian gut-associated bacteria have a profound capacity for glycan degradation that greatly exceeds our own. While the human genome encodes 17 enzymes for the digestion of dietary carbohydrates, intestinal bacteria encode anywhere from several dozen to several hundreds of these glycoside hydrolases. The glycolytic potential of an individual species influences its adaptation to the intestinal tract and its responsiveness to dietary change. Beyond fiber processing, these bacteria need to recognize and import the liberated monosaccharides and oligosaccharides from the collective catabolism of the community. Glycan recognition occurs at the cell surface, and the fit between protein and carbohydrate structure is highly specific. Many gut bacteria encode a large suite of cell-surface proteins and transporters in order to successfully compete for carbohydrate nutrition within the constantly changing glycan landscape. This critical selection event dictates the ability of these organisms to eat and thrive in their environment, yet we know little about the molecular details of this process. A mechanistic understanding of how cell surface proteins facilitate carbohydrate acquisition can lead to novel strategies for specifically targeting individual gut bacteria in order change the community to

improve human health. The long-term goal of the Koropatkin lab is to understand the molecular events that support glycan utilization within the different major Phyla of bacteria in the human gut. We have spent the past several years elucidating the unique carbohydrate uptake systems used by the Bacteroidetes. The broad glycolytic potential of these organisms is packaged into discrete polysaccharide utilization loci (PUL) that encode the necessary machinery for the degradation and import of a distinct glycan structure. PUL-encoded protein complexes are referred to as starch utilization (Sus)-like systems and all are comprised of a putative TonB-dependent transporter and two classes of carbohydrate-binding proteins: the SusD-like proteins and the surface glycan-binding lipoproteins (SGBPs). Much of our work with the complexes for the acquisition of starch and xyloglucan has revealed that the interactions of the glycan-binding proteins with the TonB-dependent transporter are more important than their ability to bind glycan. Moreover, single-molecule imaging of individual Sus-like proteins suggests that these proteins dynamically assemble at the cell surface during the catabolism of large polysaccharides. Beyond the Bacteroidetes, we are also working towards a molecular understanding of how specific Gram-positive members of the community are capable of degrading resistant starch, a highly beneficial dietary fiber that elicits enhanced butyrate which suppresses inflammation and tumorigenesis. Moving forward with our work, a critical need will be improved methodology for the detection and isolation of carbohydrate structures within the gut environment. The complexity of carbohydrate structures and their unique chemistries is a barrier for the development of high-throughput and user-friendly technologies such as those that have allowed the 'omics revolution to flourish. With enhanced glycobiology tools, we will be better equipped to not only track the carbohydrate landscape of the gut, but also study the specific protein-carbohydrate interactions that allow our gut symbionts to thrive in the intestine.

Testing Diet-Gut Microbiome Interactions: Use of Controlled Feeding Studies in Humans

Johanna W. Lampe

Public Health Sciences Division, Fred Hutchinson Cancer Research Center

Diet is a complex environmental exposure. Increasingly, the importance of diet-gut microbiome interactions in relation to health are being recognized. Diet can influence the relative abundance and activity of microbes present in the gut, and gut microbial metabolism of dietary constituents produces compounds that may have positive or adverse effects on risk for disease. The human gut microbiome responds rapidly to changes in diet composition, which provides the opportunity to use experimental studies in humans to examine the effects of diet on gut microbial community structure and activity and downstream effects on biomarkers of health and disease. Controlled feeding studies can be designed to evaluate the effects of a single nutrient or bioactive, individual foods, or dietary patterns on biomarkers or end-points of interest. Using a controlled feeding study to test a single dietary constituent or food against a standardized background diet helps to reduce variability. Feeding studies are usually conducted using parallel-arm or randomized crossover designs. Given the high degree of interindividual variation in gut microbial structure and functional capacity, a crossover design—where each individual serves as their own control—lends itself well to studying diet-gut microbiome interactions because the measured effect of the intervention is the difference in an individual participant's response to intervention and control. A crossover design is also useful in controlling for variability associated with responders and non-responders; differences in gut microbial metabolism of dietary constituents can contribute to substantial differences in circulating levels of bioactive metabolites and ultimately biologic response across individuals. Examples of application of controlled feeding study designs to research on diet-gut microbiome interactions will be presented.

Needs: Comprehensive, well-annotated metabolomics platforms that capture endogenous and exogenous compounds and their bacterial metabolites will facilitate interpretation of experimental studies of diet and the gut microbiome in humans.

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Efforts to Understand Causation in Microbiota-Host Interaction: Two Examples

Andrew Goodman

Department of Microbial Pathogenesis, Yale University

I will review our recent efforts to understand the consequences of microbiome variation. We are developing new approaches to control commensal gene expression inside the gut of living animals, which may present new opportunities to explore how dose-response and timing impact host-microbiota interactions. I will also describe our collaborative projects to understand how products of microbial metabolism impact host physiology.

Bile Acid-Microbiota Cross-Talk and Its Effects on Liver Cancer

Wei Jia

Cancer Epidemiology Program, University of Hawaii Cancer Center

Emerging evidence points to a strong association between the gut microbiota and the risk, development and progression of gastrointestinal cancers such as hepatocellular carcinoma (HCC). Bile acids are produced in the liver and metabolized by enzymes derived from intestinal bacteria, and are critically important for maintenance of a healthy gut microbiota, balanced lipid and carbohydrate metabolism, insulin sensitivity and innate immunity. Given the complexity of bile acid signaling and the direct biochemical interactions between the gut microbiota and the host, a systems biology perspective is required to understand the liver–bile acid–microbiota axis and its role in gastrointestinal carcinogenesis in order to reverse the microbiota-mediated alterations in bile acid metabolism that occur in disease states. Here we demonstrated that bile acids can activate proliferation of hepatic stellate cells (HSCs), which is a critical step in the liver fibrogenetic process, which in turn, may further lead to liver carcinogenesis. Our results showed that liver fibrosis was in direct association with significantly increased reabsorbed, hydrophobic bile acids in blood serum of 725 biopsy-confirm liver fibrosis patients with chronic hepatitis B virus infection and in liver and serum of a streptozotocin-high fat diet (STZ-HFD) induced nonalcoholic steatohepatitis-hepatocellular carcinoma (NASH-HCC) model mice. The gut microbiota alterations were closely correlated with altered bile acid levels in liver and feces in NASH-HCC mice. HFD-induced inflammation inhibited key bile acid transporters, resulting in sustained increases in intrahepatic bile acid concentrations. Reabsorbed, hydrophobic bile acids, especially DCA, TDCA and GDCA treatment significantly increased the human normal HSCs (LX-2) proliferation and the expression of fibrosis-related markers including α-smooth muscle actin (α-SMA), transforming growth factor-beta (TGF-ß), collagen type I (COL-I) and platelet-derived growth factor (PDGF) as well as TGR5. Enhancing intestinal excretion of hydrophobic bile acids in the NASH-HCC model mice by a 2% cholestyramine feeding prevented liver fibrogenesis as well as HCC development with significantly decreased expression of a-SMA, TGF-ß, COL-I , PDGF, TGR5 as well as the decreased activation of p38 MAPK, ERK1/2 signaling pathway within HSCs. Taken together, our results demonstrated that gut

microbiota-mediated intrahepatic accumulation of bile acids induces and sustains hepatocellular injury by HSC activation via a TGR5-dependent mechanism, leading to the development of liver fibrosis and HCC. Our study also highlights such novel strategy to target the gut microbiota-dependent alterations in bile acid metabolism in the context of the liver cancer prevention and therapy.

Biofilms as a Risk Factor for Human Colon Cancer

Cynthia L. Sears

Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University School of Medicine

Biofilms form in humans at sites of chronic infection and inflammation. However, if and how they contribute to, and possibly augment, the clinical impact of chronic infections is unknown. In contrast, in healthy tissues including the gut, biofilms have been infrequently identified. In the gut, biofilms are characterized as dense (>10^9 bacteria/mm^3) clusters of bacteria that invade the inner mucus layer of the colon, such that bacteria are in contact with the colonic epithelial cells. Recently, colon biofilms have been found in association with ~50% of colon tumors with a notable preponderance among tumors proximal to the hepatic flexure. Further, biofilm formation is not limited to tumors but rather, when present, biofilms appear to most likely be a feature of the entire colon, suggesting that biofilm formation on normal colonic tissue occurs before tumor initiation. In contrast, individuals undergoing screening colonoscopy display biofilms in ~10-15%. Preliminary data suggest biofilm formation is enhanced in prior or active smokers, known to have an increased risk of proximal colon cancer. Herein, the data supporting colon biofilm formation as a risk factor for colon cancer will be reviewed as will a vision of how biofilm detection may contribute to enhancing the success of screening colonoscopy as a colon cancer prevention tool.

Role of the Lung Microbiome in Respiratory Health and Disease

Gary B. Huffnagle

Division of Pulmonary and Critical Care Medicine, Department of Molecular Cell Dev Biology, Department of Microbiology and Immunology, Mary H. Weiser Food Allergy Center, University of Michigan

Chronic bacterial colonization in respiratory diseases has been traditionally evaluated by cultivation-based methods using sputum and bronchoalveolar lavage fluid, with the magnitude and type of organisms varying widely. It is now appreciated that the lung harbors viable bacteria during health ("the lung microbiome") and the lung microbiome during disease is distinct from that observed in healthy individuals. Notably, the magnitude of these changes is not captured by standard culture techniques. A major challenge for the study of the lung microbiome has been (and will likely always be) the fact that lower airway sampling is highly invasive and not amenable to serial sampling over time. Unlike studies of the gastrointestinal tract, culture-independent analyses of the airways have not identified significant numbers of routinely unculturable bacteria. Rather, these studies implicate the existence of culturable bacterial species, such as *Pseudomonas* spp. This raises the first question: do these microbes go through cycles of culturability and "unculturability" during disease? If so, this would reflect (1) a change in the nutritional environment of the lungs, (2) adaptation to host defenses and (3) a change in the metabolic activity of the bacteria. Thus, the second question is "what are these changes in the lung nutrient environment?" More recently, studies have begun to support the concept that host-derived factors during inflammation may be a driving force for adaptation and metabolic shifts in bacteria within the

microbiome of many body sites; the end result being the emergence of pathogenic strains from otherwise non-pathogenic bacterial-epithelial biofilms. The major question for this line of investigation is "are changes in the lung microbiome the *cause* of airway inflammation, the *effect* of inflammatory processes or *both*?" In cystic fibrosis, chronic obstructive pulmonary disease, interstitial pulmonary fibrosis and asthma, questions remain about the mechanism(s) underlying the persistent inflammatory/immune response, with several theories advanced, including a role for low-grade microbial infection in perpetuating inflammation. For example, bacterial products/metabolites are implicated in airway mucus hypersecretion, the major characteristic of chronic bronchitis. Our over-arching hypothesis is that inflammation changes the lung environment, which in turn, changes the lung bacterial microbiome (favoring the growth of specific species of Gammaproteobacteria), thereby creating a self-reinforcing cycle of inflammation.

Keynote III: Microbiome Interventions: From Fecal Transplants to Synthetic Microbial Therapeutics

Eric Alm

Department of Biomedical Engineering, Massachusetts Institute of Technology

Fecal transplantation is already in widespread use for recurrent Clostridium difficile infection, and numerous research studies are underway for many other diseases. I will explore the mechanism of fecal transplantation using genomic assays, and discuss efforts to create a next-generation of microbial therapeutics based on synthetic microbial cultures.

Towards a Metagenomic Basis of Therapeutics

Peter Turnbaugh

Department of Microbiology and Immunology, University of California, San Francisco

Although the importance of human genetic polymorphisms in therapeutic outcomes is well established, the role of our "second genome" (the microbiome) has been largely overlooked. I will briefly highlight notable studies conducted over the past 5-10 years that have shed light on the mechanisms that link the human gut microbiome to the efficacy and toxicity of xenobiotics, including drugs, dietary compounds and environmental toxins. The challenges are immense, requiring inter-disciplinary scientific teams working at the interface of chemistry and microbiome research, and a consideration of far more variables than traditionally included in pharmacological models. However, the potential benefits are inspiring. Continued progress in this area could enable more precise tools for predicting patient responses and for the development of a new generation of therapeutics based on, or targeted at, the gut microbiome. Indeed, the admirable goal of precision medicine may require us to first understand the microbial pharmacists within.

Gut Microbial Metabolites and Cancer Prevention

Scott J. Bultman

Department of Genetics and Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill

Gut microbiota have a prodigious metabolic capacity and convert dietary factors and digestive components into oncometabolites and tumor-suppressive metabolites that influence cancer risk. Our lab is particularly interested in butyrate, which is a short-chain fatty acid produced by bacterial fermentation of dietary fiber. Butyrate is noteworthy because it has energetic and epigenetic functions in colonocytes and tumor-suppressive properties in colorectal cancer cell lines. We utilized gnotobiotic mouse models of colorectal cancer colonized with wild-type or mutant strains of a butyrate-producing bacterium to demonstrate that fiber does have a tumor-suppressive effect but in a microbiota- and butyrate-dependent manner. Furthermore, due to the Warburg effect, butyrate was metabolized less in tumors where it accumulated and functioned as an HDAC inhibitor to stimulate histone acetylation and affect cell proliferation and apoptosis. To support the relevance of this mechanism in human cancer, we demonstrated that butyrate and histone acetylation levels are elevated in colorectal adenocarcinomas compared to normal colonic tissues. These studies highlight several challenges and opportunities for microbiome research in general:

- **More non-targeted metabolomics:** Dysbiosis is often associated with different microbiota that have equivalent functions due, in part, to the production of common metabolites associated with a disease state.
- **Pleiotropic metabolites and multiple mechanisms:** Understanding the mode of action will be challenging for some metabolites. For example, butyrate is an energy source, epigenetic regulator, and signaling factor that exerts cell autonomous effects within cancer cells while also regulating gut barrier function and the induction of Treg cells.
- **Organotypic tissue constructs co-cultured with microbiota:** Due to limitations of gnotobiotic mouse models, there is a need for improved human organoid platforms that can be efficiently co-cultured with microbiota. To probe relevant host-microbe interactions in the gut, it will be necessary to deliver a sharp oxygen gradient to maintain a normoxic intestinal crypt juxtaposed with obligate anaerobes.
- **Combinatorial human studies:** Human prospective-cohort studies that evaluate diet could potentially be made more reproducible by integrating them with microbiome and GWAS or exome sequencing. For example, a high-fiber diet may protect against a subset of individuals who share a certain combination of microbiota and genetic variants. Dietary interventions are expected to be mutually beneficial for microbiome and genetic research.

Microbiomes and Phenotypes: Impact, Restoration and Transfer

Maria Gloria Dominguez-Bello

Department of Medicine, New York University School of Medicine

Microbiont bacteria have coevolved with their hosts, and are tolerated by the host immune system, playing a role in healthy development. Humans are experiencing increasing urbanization with increasing incidences of immune and metabolic disorders (asthma, T1D, allergies, obesity) with a concomitant reduction in their gut microbiota diversity.

C-sections and early antibiotic exposure increase the risk of these urban associated diseases and the challenge remains to restore after microbiota-impacting interventions to rescue normal phenotypes and prevent disease. A rational use of medical practices that disturb the microbiota, together with restoration are urgently needed to arrest and prevent the current disease trend.

Allogeneic Hematopoietic Stem Cell Transplantation: Clinical Outcomes, Intestinal Bacteria, and Potential Mechanisms

Robert Jenq

Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

Common complications of allogeneic hematopoietic stem cell transplantation have long been known to be linked with intestinal commensal bacteria and use of antibiotics, in particular outcomes including neutropenic fever and intestinal graft-versus-host disease. Characterization of the intestinal microbiome in patients and animal models has revealed new insights into this relationship. Developing approaches to target the microbiome in the allogeneic hematopoietic stem cell transplant population represents a new opportunity to improve patient outcomes for this important treatment modality.

Microbiota-Mediated Defense Against Antibiotic-Resistant Infections

Eric G. Pamer

Division of Subspeciality Medicine, Memorial Sloan Kettering Cancer Center

Infections caused by antibiotic-resistant bacteria generally begin with colonization of mucosal surfaces, in particular the intestinal epithelium. The intestinal microbiota provides resistance to infection with highly antibiotic-resistant bacteria, including Vancomycin Resistant Enterococcus (VRE), Klebsiella pneumoniae and *Clostridium difficile*, the major cause of hospitalization-associated diarrhea. Metagenomic sequencing of the murine and human microbiota following treatment with different antibiotics is beginning to identify bacterial taxa that are associated with resistance to Vancomycin resistant Enterococcus faecium (VRE) and *Clostridium difficile* infection. By treating mice with different antibiotics that result in distinct microbiota changes and lead to varied susceptibility to *C. difficile*, we correlated loss of specific bacterial taxa with development of infection. Using a workflow involving mouse models, clinical studies, metagenomic analyses and mathematical modeling, we identified a probiotic candidate that corrects the microbiome deficiency responsible for susceptibility to *C. difficile* infection. Using a similar strategy, we demonstrated that oxygen-tolerant members of the microbiota

are ineffective at eliminating VRE while administration of obligate anaerobic commensal bacteria to mice results in a billion-fold reduction in the density of intestinal VRE colonization. We have identified specific bacterial species, including *Blautia producta* and *Clostridium bolteae,* that prevent intestinal colonization with VRE and lead to its clearance from the gut. Our studies indicate that obligate anaerobic bacteria that can be retrieved from the commensal microbiota enable clearance of intestinal VRE colonization and provide resistance to *C. difficile* infection. These bacterial species may provide novel approaches to prevent the spread of highly antibiotic-resistant bacteria. A critical gap for this field is the incomplete representation and characterization of human-microbiota-derived commensal bacterial species in publically accessible bio-repositories.

Engineering Biological Computers for Human Health Applications

Timothy Lu

Synthetic Biology Group, Department of Electrical Engineering and Computer Science and Department of Biological Engineering, Massachusetts Institute of Technology

Over the last 50 years, exponential increases in our ability to manipulate electrons and engineer electronic systems spawned the information technology revolution. Similarly rapid improvements in technologies for reading and writing DNA are now transforming our capacity to engineer biological systems. Leveraging these technologies, synthetic biology is an emerging discipline for designing biological systems with novel functionalities. This field has opened up new strategies for interrogating and understanding biology, as well as for diagnosing and treating human diseases. I will discuss several relevant examples where we have created digital and analog synthetic gene circuits for sophisticated sense-and-respond behaviors, as well as genomically encoded memory devices. We are advancing synthetic gene circuits into multiple microbial chassis for the ultimate goal of microbiome engineering.

Connecting the Gut Microbiome and Cancer Through Circadian Rhythms

Eugene B. Chang

Department of Medicine and Microbiome Medicine Program of the University of Chicago

Circadian rhythms (CR) are essential for most life forms, regulating behavioral, physiological, genetic, and metabolic functions. Disruption of CR by western type diets, sleep disruption, and lifestyle changes that are often associated with the development of obesity and type II diabetes can dramatically alter tissue homeostasis by perturbing energy balance, DNA repair mechanisms, and cell growth and differentiation to promote cancer initiation and progression. Recently, several reports have shown a potential role of the gut microbiome in cancer development, although there is a large gap in our understanding of mechanisms and mediators underlying these actions. The need and challenge is to develop better experimental systems to study the gut microbiome in a more physiological and disease context. Traditionally, the belief has been that circadian clocks and downstream targets are primarily driven by light and dark visual cues received by the suprachiasmatic nucleus. However, we showed an additional key element involved in maintaining host circadian rhythms, the gut microbiome, which potentially links cancer, diet-induced obesity, and the gut microbiome. Despite persistence of light-dark signals, germ-free mice fed low or high-fat diets exhibit markedly impaired central and hepatic circadian clock gene expression and do not gain weight compared to conventionally raised counterparts. Examination of gut microbiota in conventionally raised mice showed differential diurnal variation in

microbial structure and function dependent upon dietary composition. Additionally, specific microbial metabolites induced under low- or high-fat feeding, particularly short-chain fatty acids, but not hydrogen sulfide, directly modulate circadian clock gene expression within hepatocytes. These results underscore the ability of microbial-derived metabolites to regulate or modify central and hepatic circadian rhythm and host metabolic function. These findings therefore provide additional insights into how western diets that cause gut dysbiosis, loss of microbial drivers and signals, and disruption of host circadian rhythms can potentially contribute to the cancer initiation and progression. They also suggest that microbiome-derived interventions to restore host circadian rhythms can be used to decrease risk of obesity and cancer.

SPEAKER BIOSKETCHES

Eric Alm, Ph.D.

Department of Biomedical Engineering, Massachusetts Institute of Technology

Dr. Alm earned his bachelor's degree from the University of Illinois at Urbana-Champaign, his master's degree from the University of California, Riverside, and his Ph.D. degree from the University of Washington, Seattle. He held a postdoctoral appointment at the University of California, Berkeley, and the Lawrence Berkeley National Laboratory before joining the faculty at the Massachusetts Institute of Technology. Dr. Alm's research group is an interdisciplinary team of computer scientists, computational biologists, molecular biologists, and microbial ecologists.

Elhanan Borenstein, Ph.D.

University of Washington and Santa Fe Institute

Dr. Borenstein is an Associate Professor in the Department of Genome Sciences and an Adjunct Associate Professor in the Department of Computer Science and Engineering at the University of Washington and an External Professor at the Santa Fe Institute. His research takes a systems-level approach to developing computational models and tools to gain a better understanding of the structure and function of the microbiome. Dr. Borenstein received a bachelor's degree in physics and computer science and a doctoral degree in computer science from Tel-Aviv University, Israel, and conducted postdoctoral work at Stanford University.

Robert A. Britton, Ph.D.

Department of Molecular Virology and Microbiology, Alkek Center for Metagenomics and Microbiome Research, Baylor College of Medicine

Dr. Britton is a Professor in the Department of Molecular Virology and Microbiology and a member of the Alkek Center for Metagenomics and Microbiome Research at Baylor University's College of Medicine. He directs the Therapeutic Microbiology Laboratory that is focused on the use of microbes to prevent and treat human disease. Currently funded research projects in the laboratory range from the study of how traditional probiotic strains can ameliorate osteoporosis to how intestinal microbial communities resist invasion by the diarrheal pathogen *Clostridium difficile*. Dr. Britton's laboratory has made several advances in the development of genetic and microbial growth platforms to aid in the understanding of how microbes promote health and disease. These include the development of precision genome engineering technologies for lactic acid bacteria and the development of human fecal minibioreactor arrays to study the function of microbial communities in a high-throughput manner. He received a bachelor's degree in biology from the University of Nebraska-Lincoln and a doctoral degree in cell and molecular biology from Baylor University College of Medicine. After performing postdoctoral training at the Massachusetts Institute of Technology, Dr. Britton started his own laboratory at Michigan State University. After rising to the rank of professor in 2014, he moved to his current position at the Baylor University College of Medicine.

Gregory A. Buck, Ph.D.

Center for the Study of Biological Complexity, Department of Microbiology and Immunology, Virginia Commonwealth University

Dr. Buck is a Professor of Microbiology and Immunology at Virginia Commonwealth University (VCU). He obtained his bachelor's degree in genetics from the University of Wisconsin-Madison, and his master's and doctoral degrees in microbiology and immunology from the University of Washington-Seattle studying the toxinogenic bacteriophages of *Corynebacterium diphtheriae*. Dr. Buck did postdoctoral research at the Institut Pasteur in Paris studying the genetics of antigenic variation in African trypanosomes and subsequently joined the faculty in the Department of Microbiology and Immunology at VCU. He founded and directs VCU's Nucleic Acids Research Facilities, which maintains VCU's Next Generation Sequencing infrastructure, and the Center for High Performance Computing, which provides research computing capacity to VCU's investigators. Dr. Buck founded the Center for the Study of Biological Complexity in 2000 under the umbrella of VCU Life Sciences and directed that unit until 2017. His recent work focuses on high-throughput microbial genomics and metagenomics, with a focus on women's health.

Scott J. Bultman, Ph.D.

Department of Genetics and Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill

Dr. Bultman is interested in investigating the role of SWI/SNF chromatin-remodeling complexes in mammalian development and disease and the roles of dietary fiber, gut microflora, and epigenetic events that protect against colorectal cancer.

Eugene B. Chang, M.D.

Department of Medicine and Microbiome Medicine Program of the University of Chicago

Dr. Chang is the Martin Boyer Chaired Professor in the Department of Medicine and Director of the Microbiome Medicine Program at the University of Chicago. His research focuses on host-microbe interactions that relate to states of health and disease. These studies fall into two primary areas: metabolic diseases (diet-induced obesity) and complex immune disorders (e.g., inflammatory bowel diseases). Using a combination of 'omic technologies, new data science approaches, and gnotobiotic mouse models, Dr. Chang has been examining the role and effects of dietary and environmental factors that promote risk for "Western" culture-related diseases (i.e., disorders that were uncommon or rare a century ago but are now occurring with alarming frequency). He received his bachelor's degree from the Johns Hopkins University and his M.D. degree from the University of Chicago where he also completed his training in internal medicine and gastroenterology.

Mildred Cho, Ph.D.

Center for Biomedical Ethics and Professor, Departments of Pediatrics and Medicine, Stanford University

Dr. Cho is a Professor in the Division of Genetics of Stanford's Department of Pediatrics. For the past 10 years she has been the Principal Investigator of an NIH-funded Center for Excellence in Ethical, Legal, and Social Implications Research and established the Center for Integration of Research on Genetics and Ethics. As Director of this Center, Dr. Cho has led a number of research groups that are conducting studies to identify the ethical issues associated with the translation of biomedical research to clinical application. This research aims to inform research policy and public health policy on the translation of biomedical research into clinical practice and training. She also has conducted interdisciplinary normative and empirical work on research ethics topics, including ethical issues arising from new biomedical technologies, the impact of intellectual property policy and financial conflicts of interest on biomedical research (in particular on genetic testing and research), ethical issues in genetic and genomic research and clinical application, and patient and professional attitudes toward comparative effectiveness research. A major portion of Dr. Cho's recent work has focused on the ethical issues raised by biobanking, precision health research, and the use of clinically derived data and biosamples in racially and ethnically diverse populations.

Gautam Dantas, Ph.D.

Departments of Pathology and Immunology, Biomedical Engineering and Molecular Microbiology, Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis

Dr. Dantas is an Associate Professor in the Department of Pathology and Immunology, the Department of Biomedical Engineering, and the Department of Molecular Microbiology in the School of Medicine, Washington University, St. Louis. His research interests are at the interface of microbial genomics, biochemistry, systems biology, and computational biology to understand, harness, and engineer the biochemical processing potential of microbial communities. Dr. Dantas' group currently focuses on (1) understanding the evolution and exchange of antibiotic resistance amongst diverse microbial communities, (2) systems-guided design of novel antibiotic and probiotic therapies, and (3) engineering microbial catalysts to produce value chemicals such as biofuels. He received a bachelor's degree in biology and chemistry from Macalester College, his doctoral degree in biochemistry from the University of Washington under the mentorship of David Baker, and postdoctoral training in microbial genomics from Harvard Medical School under the mentorship of George Church. In 2009 Dr. Dantas joined the Department of Pathology and Immunology at the Washington University School of Medicine, St. Louis as Assistant Professor.

Maria Gloria Dominguez-Bello, Ph.D.

Department of Medicine, New York University School of Medicine

Dr. Dominguez-Bello's research has focused for the past years on the microbiota function in vertebrate animals and human beings; microbiota development and the impact of modern practices; and integrating data from microbiology, genomics/metagenomics, ecology, physiology, anthropology, architecture, environmental engineering, and biostatistics to address broad questions on host-microbial interactions in different environments. The focus is on how these interactions drive microbial evolution, diversity, and symbiosis. She studies the bacterial microbiota in vertebrates, including birds and

mammals and has led studies using Nextgen sequencing of the human microbiome in people with different levels of integration into Western lifestyles in the Amazon region and southern Africa. Dr. Dominguez-Bello's group is a strong team of collaborators that include, among others, Rob Knight (University of Colorado), Jeff Gordon (Washington University), Martin Blaser (New York University), Suzanne Tringe (U.S. Department of Energy Joint Genome Institute), Gary Andersen (Lawrence Berkeley National Laboratory), Monica Contreras (Venezuelan Inst Sci Research-IVIC), Magda Magris (Amazonic Center for Research In Tropical Diseases, CAICET, Venezuela), Jean Hernandez (INS Loreto, Iquitos, Peru), and Henrique Pereira (University Federal Amazonas, Manaus, Brazil).

Sharon M. Donovan, Ph.D., R.D.

Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign

Dr. Donovan is the Melissa M. Noel Endowed Professor of Nutrition and Health in the Department of Food Science and Human Nutrition, Division of Nutritional Sciences, University of Illinois at Urbana-Champaign. Her research focuses on how dietary intake influences neonatal development in human infants. For over 20 years, her laboratory has utilized the piglet model to study how early-life nutrition shapes immune, gut, cognitive, and microbiome development. Dr. Donovan also uses the piglet to model diarrhea diseases, total parenteral nutrition-induced gut atrophy, and colitis to evaluate nutritional and probiotic strategies to prevent and ameliorate detrimental effects of early-life insults. Dr. Donovan is now evaluating how human milk oligosaccharides and other dietary prebiotics regulate the intestinal microbiome and metagenome. She received her bachelor's degree in nutrition science and her doctoral degree in nutrition from the University of California, Davis, followed by postdoctoral work in pediatric endocrinology at the Stanford University School of Medicine.

Pieter Dorrestein, Ph.D.

Departments of Pharmacology and Pediatrics, University of California, San Diego

Dr. Dorrestein is a Professor at the University of California, San Diego (UCSD). He is trained as a chemist with a focus on understanding how microbes make amino acids, vitamins, and other small molecules such as virulence factors, quorum sensors, and therapeutically valuable natural products. Dr. Dorrestein is Director of the Collaborative Mass Spectrometry Innovation Center and a Co-Director of the Institute for Metabolomics Medicine in the Skaggs School of Pharmacy and Pharmaceutical Sciences and Department of Pharmacology and Pediatrics. Since his arrival at UCSD in 2006, he has been pioneering the development of mass spectrometry methods to study the chemical/ecological crosstalk between populations of microorganisms, including host interactions, for agricultural, diagnostic, clinical, and therapeutic applications. For a more detailed biography see http://www.nature.com/news/the-man-who-can-map-the-chemicals-all-over-your-body-1.20035.

Angela Douglas, Ph.D.

Department of Entomology and Department of Molecular Biology and Genetics, Cornell University

Dr. Douglas is the Daljit S. and Elaine Sarkaria Professor of Insect Physiology and Toxicology, Department of Entomology, Cornell University, where her research goal is to understand how resident microorganisms shape host nutritional health. Her research combines genetic and genomic approaches with physiological analyses to investigate the host-microbial interactions that promote (and occasionally impair) nutritional health at the level of the GI tract and whole animal. Dr. Douglas studies the *Drosophila*-gut microbiota model and associations involving bacteria that are subject to genomic deterioration. Her laboratory combines genome- and metagenome-based strategies (whole-genome sequencing, genotyping-by-sequencing, GWAS, and metagenome shotgun sequencing), and metabolic approaches to understand nutritional interactions with the host. She received her bachelor's degree in zoology from Oxford University (UK) and her doctoral degree in microbiology from Aberdeen University (UK), followed by postdoctoral work in biological sciences at both Oxford and the University of East Anglia (UK).

Andrew Gewirtz Ph.D.

Institute for Biomedical Sciences, Georgia State University

Dr. Gewirtz received his doctoral degree in biochemistry from the Boston University School of Medicine in 1996. He is now a professor at Georgia State University. Dr. Gewirtz specialized in research on innate immunity, microbiome, intestinal inflammation, and obesity/diabetes. Inflammation plays a central role in many disease states, and his goal is to understand the normal mechanisms by which proinflammatory signals protect against microbes and discern how they go awry in disease states. The primary area of focus is the intestinal epithelium, one of human beings' major interfaces with the outside world. This interface is very heavily colonized with gram-negative bacteria and yet permits absorption of life-sustaining nutrients while protecting the tissues below from microbial onslaught. In addition to serving as a highly selective barrier, the intestinal epithelium regulates the microbial and immunological communities in its midst. Specifically, the epithelia shape the composition and locale of intestinal bacteria by producing antimicrobial substances and recruiting immune cells to efficiently clear bacteria that disturb equilibrium in the intestine. These pathways can go awry and result in chronic inflammation if the intestine "inherits" an aberrant microbial community and/or immune dysfunction.

Mahmoud Ghannoum, Ph.D., M.B.A.

Case Western Reserve University and University Hospital Cleveland Medical Center

Dr. Ghannoum received his master of science degree in medicinal chemistry and his doctoral degree in microbial physiology from the University of Technology in England and his master of business administration degree from the Weatherhead School of Management at Case Western Reserve University (CWRU). He is a tenured Professor and Director of the CWRU's Center for Medical Mycology and University Hospitals Cleveland Medical Center, where he established a multidisciplinary Center of Excellence that combines basic and translational research investigating microbes from the test tube to the bedside. Dr. Ghannoum is also a fellow of the Infectious Diseases Society of America and past President of the Medical Mycological Society of the Americas (MMSA). In 2016 he received the Rhoda Benham Award for his continuous outstanding and meritorious contributions to medical mycology from

MMSA and the Freedom to Discover Award from Bristol-Myers Squibb for his work on microbial biofilms. In 2017 Dr. Ghannoum was inducted as a fellow of the American Academy of Microbiology.

Andrew Goodman, Ph.D.

Department of Microbial Pathogenesis, Yale University

Dr. Goodman is an Associate Professor in the Department of Microbial Pathogenesis and Microbial Sciences Institute at Yale University. His laboratory works to understand the mechanisms of cooperation and competition in the gut microbiome and how gut microbiome variation impacts drug metabolism.

Jeffrey I. Gordon, M.D.

Center for Genome Sciences and Systems Biology, and Center for Gut Microbiome and Nutrition Research, Washington University School of Medicine, St. Louis

Dr. Gordon is the Dr. Robert J. Glaser Distinguished University Professor and Director of both the Center for Genome Sciences and Systems Biology1 and the Center for Gut Microbiome and Nutrition Research at the Washington University School of Medicine, St. Louis. He is one of the founding figures of human microbiome research, whose lab has made many pivotal contributions to our understanding of the role of the microbiome in obesity and malnutrition over the past 20 years. Dr. Gordon's lab has pioneered the use of gnotobiotic animals for demonstrating causal roles for the microbiome in obesity and malnutrition and for studying nutrient-microbe-host interactions, opening the possibility of microbiologically informed dietary interventions to treat these disorders. His lab has developed many methods for manipulating the microbiome and analyzing its activities, which have been widely adopted throughout the human microbiome research community. Dr. Gordon received his A.B. degree from Oberlin College, his M.D. degree from the University of Chicago, and postdoctoral training in the Laboratory of Biochemistry at the National Cancer Institute, National Institutes of Health (NIH). He completed a fellowship in gastroenterology at the Washington University School of Medicine, St. Louis and has subsequently spent his entire academic career there.

Gary B. Huffnagle, Ph.D.

Division of Pulmonary and Critical Care Medicine, Department of Molecular Cell Dev Biology, Department of Microbiology and Immunology, Mary H. Weiser Food Allergy Center, University of Michigan

The overall goals of Dr. Huffnagle's current research are to identify and delineate the interactions between the microbiome (lung and gut) and the immune system. Using animal models, clinical samples, and in vitro assays, his group is investigating host-microbiome interactions in the control of pulmonary inflammation, allergic responses, and infectious disease. This requires an interdisciplinary approach that combines research in pathophysiology, immunology, microbiology, microbial ecology, and computational biology. The first two decades of Dr. Huffnagle's research career were dedicated to understanding the mechanisms underlying how the immune system eliminates microbes from the lungs and other mucosal sites. In the past 10 years, his laboratory brought in new technologies and approaches to address the biology of the microbiome and its interplay with the immune system. He is also the Chair of the intercollege, interdepartmental undergraduate microbiology program at the University of Michigan and teaches courses in microbial pathogenesis, bacteriology, and microbial

genomics. Dr. Huffnagle's lab's current projects include studies of host-microbiome interactions in both mouse models of inflammation/disease and in human disease.

Curtis Huttenhower, Ph.D.

T.H. Chan Harvard School of Public Health and Broad Institute

Dr. Huttenhower is an Associate Professor of Computational Biology and Bioinformatics at the T.H. Chan Harvard School of Public Health and an Associate Member at the Broad Institute. He was an analysis lead in the NIH Human Microbiome Project and currently co-leads the "HMP2" Center for Characterizing the Gut Microbial Ecosystem in Inflammatory Bowel Disease and directs the T.H. Chan Harvard School of Public Health's Microbiome Analysis Core. Dr. Huttenhower's lab focuses on computational methods for functional analysis of microbial communities, as well as microbiome epidemiology to link microbial community function to public health. This includes systems biology reconstructions integrating metagenomic, metatranscriptomic, and other microbial community 'omics; the human microbiome in autoimmune disease such as inflammatory bowel disease; and its potential as a diagnostic tool and point of therapeutic intervention.

Robert Jenq, M.D.

Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

Dr. Jenq received his M.D. degree from Oregon Health & Science University and completed his clinical training in internal medicine and medical oncology at Duke University and Memorial Sloan Kettering Cancer Center. He is an Assistant Professor at The University of Texas MD Anderson Cancer Center, in the Departments of Genomic Medicine and Stem Cell Transplantation. Dr. Jenq's research aims to improve outcomes for patients undergoing hematopoietic cell transplantation, with a particular focus on the intestinal microbiota and how changes in the composition of intestinal bacterial commensals can impact on clinical outcomes. He has published more than 20 manuscripts on this topic since 2010, including 5 first/last-author primary manuscripts.

Wei Jia, Ph.D.

Cancer Epidemiology Program, University of Hawaii Cancer Center

Dr. Jia is a Professor and member in the Cancer Epidemiology Program at the University of Hawaii Cancer Center (UHCC). His research interest involves carbon source metabolism and its regulation in cancer cells as well as the molecular mechanisms that link metabolic disruptions in gut microbial-host co-metabolism to metabolic disorders and gastrointestinal cancer. Several research projects are being conducted in Dr. Jia's group to decipher the complex metabolic interactions in gut-liver-brain axis and regulation of cancer cell metabolism. In addition, he directs a well-recognized metabolomics laboratory (currently as one of the UHCC shared resources). Over the past 13 years, Dr. Jia's lab has developed many metabolomics technologies and protocols, focusing on the quantitative analysis of endogenous small-molecule metabolites and trace elements from biological specimens including blood, urine, saliva, and tissues of experimental animals and human subjects. Many of these technologies have been applied in clinical and translational research, involving (1) unbiased metabolic profiling and data mining, metabolite annotation and biological interpretation using combined high-sensitivity, high-throughput

LC-MS-MS and GC-MS platforms; (2) targeted and quantitative analysis of metabolic rates and pathways using isotope-labeled common substrates such as glucose and cholate; (3) classification and prediction of disease phenotypes based on their unique metabolic signatures and biomarkers for patient stratification and personalized treatment; and (4) novel methodologies to delineate the host-gut microbe co-metabolism of diets and multicomponent herbal medicines, such as polypharmacokinetics and gut microbial metabolomics.

Rob Knight, Ph.D.

Departments of Pediatrics, Computer Science and Engineering, University of California, San Diego

Dr. Knight is the founding Director of the Center for Microbiome Innovation and Professor of Pediatrics and Computer Science and Engineering at University of California, San Diego. Before that, he was Professor of Chemistry and Biochemistry and Computer Science in the BioFrontiers Institute of the University of Colorado Boulder, and an Howard Hughes Medical Institute Early Career Scientist. Dr. Knight is a fellow of the American Association for the Advancement of Science and of the American Academy of Microbiology. In 2015 he received the Vilceck Prize in Creative Promise for the Life Sciences. Dr. Knight is the author of "Follow Your Gut: The Enormous Impact of Tiny Microbes" (Simon & Schuster, 2015) and coauthor of "Dirt is Good: The Advantage of Germs for Your Child's Developing Immune System (St. Martin's Press, 2017). He spoke at TED in 2014. Dr. Knight's lab has produced many of the software tools and laboratory techniques that enabled high-throughput microbiome science, including the QIIME pipeline (cited some 8,000 times as of this writing) and UniFrac (cited around 5,000 times). He is cofounder of the Earth Microbiome Project, the American Gut Project, and the company Biota, Inc., which uses DNA from microbes in the subsurface to guide oilfield decisions. Dr. Knight's work has linked microbes to a range of health conditions including obesity and inflammatory bowel disease, has enhanced our understanding of microbes in environments ranging from the oceans to the tundra, and has made high-throughput sequencing techniques accessible to thousands of researchers around the world. He can be followed on Twitter (@knightlabnews) or on his website http://knightlab.ucsd.edu/.

Nicole Koropatkin, Ph.D.

Department of Microbiology and Immunology, University of Michigan

Dr. Koropatkin received her doctoral degree in biochemistry from the University of Wisconsin in 2004. Trained in structural enzymology in the lab of Hazel Holden, her graduate work focused on the enzymes involved in *O*-antigen deoxysugar biosynthesis in *Salmonella typhi*. After finishing her training, Dr. Koropatkin moved to the laboratory of Thomas Smith at the Donald Danforth Plant Science Center in St. Louis. She received a National Research Service Award to determine the structural basis for nitrate and bicarbonate discrimination within the ABC transport systems of *Synechocystis PCC 6803*. After completing this study, Dr. Koropatkin teamed up with Eric Martens from the Jeffrey Gordon lab at Washington University, St. Louis to investigate the structures of the novel proteins encoded within Bacteroidetes polysaccharide utilization loci. In 2009 she moved to the University of Michigan Medical School to continue this work as a Research Assistant Professor. In January 2014 she moved into a tenure-track position as an Assistant Professor in the Microbiology and Immunology Department. The Koropatkin lab studies the structural biology of glycan capture by a variety of human gut bacteria.

Johanna W. Lampe, Ph.D., R.D.

Public Health Sciences Division, Fred Hutchinson Cancer Research Center

Dr. Lampe is a Full Member and Associate Director of the Public Health Sciences Division at Fred Hutchinson Cancer Research Center (FHCRC) and a Research Professor in the Department of Epidemiology at the University of Washington in Seattle. She received her doctoral degree in nutritional sciences, with a minor in biochemistry, from the University of Minnesota and trained as a postdoctoral fellow in epidemiology at the University of Minnesota before joining the faculty at FHCRC . Dr. Lampe's research focuses on the effect of diet constituents on cancer susceptibility in humans and the effects of human and gut microbial genetic variation on response to diet. Her lab studies the modifying effects of the gut microbiome on phytochemical metabolism and disease risk. In 2014 Dr. Lampe received the American Society for Nutrition Mary Swartz Rose Senior Investigator Award for research on the safety and efficacy of bioactive compounds for human health.

Timothy Lu, M.D., Ph.D.

Synthetic Biology Group, Department of Electrical Engineering and Computer Science and Department of Biological Engineering, Massachusetts Institute of Technology

Dr. Lu is an Associate Professor leading the Synthetic Biology Group in the Department of Electrical Engineering and Computer Science and the Department of Biological Engineering at the Massachusetts Institute of Technology (MIT). He received his bachelor's and master's degrees in engineering from MIT, and his M.D. and Ph.D. degrees from the Harvard-MIT Health Sciences and Technology Program. Dr. Lu is a core member of the MIT Synthetic Biology Center and a cofounder of multiple biotechnology companies innovating new diagnostic and therapeutic technologies for human health, including Sample6, Senti Biosciences, Synlogic, Eligo Bioscience, MBcure, and Engine Biosciences. His research focuses on engineering platforms for computing and memory in living cells and applying these to create adaptive medicines as next-generation cell and gene therapies for important human diseases. Dr. Lu's work also includes developing novel technology platforms to interrogate and correct diseased cell states. He is a recipient of the American Chemical Society's Synthetic Biology Young Investigator Award, the Biochemical Engineering Journal Young Investigator Award, the NIH New Innovator Award, the Presidential Early Career Award for Scientists and Engineers, and the Ellison Medical Foundation New Scholar in Aging Award, among others.

Howard Ochman, Ph.D.

Department of Integrative Biology, University of Texas at Austin

Dr. Ochman is a Professor in the Department of Integrative Biology at the University of Texas at Austin (UTA). Originally trained as a population geneticist at the University of Rochester, where he received his doctoral degree in 1984, technical advances in molecular biology prompted his switch to studying the organization and evolution of bacterial genomes, and for the past three decades, he has been investigating molecular evolution and the diversity of interactions among microbes. After a postdoctoral stint in the Department of Biochemistry at the University of California, Berkeley, Dr. Ochman worked as a research scientist on the Human Genome Project and in 1987 moved to Washington University, St. Louis to study the evolution of bacterial pathogenesis. Prior to joining the faculty at UTA, he held faculty

appointments at the University of Rochester (1991-1998), University of Arizona (1998-2010), and Yale University (2010-2013).

Eric G. Pamer, M.D.

Division of Subspeciality Medicine, Memorial Sloan Kettering Cancer Center

Dr. Pamer received his bachelor's degree in biology in 1977 from Case Western Reserve University in Ohio. He later received his M.D. degree in 1982 from Case Western Reserve Medical School. Dr. Pamer heads the Division of Subspecialty Medicine at Memorial Sloan Kettering Cancer Center MSKCC), and his laboratory's research efforts have focused on infections associated with cancer therapy. In particular, he has investigated the intestinal microbiota and its role in defense against infections caused by antibiotic-resistant pathogens such as *Clostridium difficile*, Vancomycin-resistant Enterococcus, and Klebsiella pneumonia. Dr. Pamer's group was the first to demonstrate that patients undergoing allogeneic hematopoietic stem cell transplantation experience dramatic changes in the composition of the intestinal microbiota, generally with drastic losses of a wide range of bacterial taxa associated with health, leaving the patient vulnerable to a wide range of pathogens. Recent studies from his group have demonstrated a marked increase in posttransplant mortality associated with loss of intestinal microbiota diversity. Dr. Pamer has established collaborations with the Computational Biology Program at MSKCC that enables his team to analyze 16S and metagenomic sequences obtained from murine intestinal samples and from human fecal samples. His team also collaborates with the Bone Marrow Transplant Service at Memorial Hospital and has obtained fecal samples from patients undergoing allo-HSCT. The Lucille Castori Center Molecular Microbiology Core Laboratory, of which he is a director, has developed an efficient and systematic approach to cataloging and extracting clinical and experimental samples, purifying and sequencing DNA, and performing analyses to compare the microbiota in different samples and to quantify differences in microbiota composition. MSKCC's core laboratories, clinical facilities, and clinical research infrastructure have enabled his team to develop an Institutional Review Board and a U.S. Food and Drug Administration-approved randomized clinical trial to test the effectiveness of autologous fecal microbiota transplantation in preventing *C. difficile* colitis in patients following allo-HSCT. Dr. Pamer has mentored more than 30 postdoctoral fellows and 10 graduate students over the past 20 years and has extensive experience participating in graduate and clinical training programs.

Andrew D. Patterson, Ph.D.

Center for Molecular Toxicology and Carcinogenesis, Department of Veterinary and Biomedical Sciences, Pennsylvania State University

Dr. Patterson is an Associate Professor of Molecular Toxicology at the Pennsylvania State University and is the Scientific Director of Metabolomics. He graduated from the joint NIH and George Washington University graduate partnerships program in 2006 and completed a postdoctoral fellowship as a Pharmacology Research Associate in the Laboratory of Metabolism under Dr. Frank Gonzalez at the National Cancer Institute in 2011. Dr. Patterson joined the Center for Molecular Toxicology and Carcinogenesis at Pennsylvania State University in 2011. He and his students, postdocs, and collaborators focus on understanding the host-metabolite-microbiota communication network, specifically how the manipulation of gut microbiota by diet and/or xenobiotics impacts host metabolites (e.g., bile acids, short-chain fatty acids), their metabolism, and how these co-metabolites interact with host nuclear/soluble receptors (e.g., farnesoid X receptor, aryl hydrocarbon receptor). The lab employs a

variety of tools, including nuclear magnetic resonance- and mass spectrometry-based metabolomics, genomics, and conventional and gnotobiotic transgenic mice, to facilitate its study of these pathways and understand their impact on human health and disease.

Mary Ellen Perry, Ph.D.

Office of Strategic Coordination, Office of the Director, NIH

Dr. Perry is a Program Leader in the Office of Strategic Coordination (OSC) in the Office of the NIH Director. OSC is the home of the Common Fund, which supports trans-NIH programs that foster the missions of multiple Institutes and Centers by changing important paradigms, making critical discoveries, developing needed technologies, and disseminating the resulting products and knowledge. Dr. Perry provides guidance and oversight to Common Fund programs, which are managed directly by NIH Institute and Center staff members. She has been the Program Leader for the Human Microbiome Project since its inception in 2007. In addition, she helps lead the Science of Behavior Change Program, the Regulatory Science Program, and the Undiagnosed Disease Network. Dr. Perry received a bachelor's degree in animal science from the University of New Hampshire after which she pursued doctoral studies at The University of North Carolina at Chapel Hill. Following postdoctoral stints at the Imperial Cancer Research Fund (now part of Cancer Research, UK) and Princeton University, she established a cancer research program at the University of Wisconsin, reaching the rank of Associate Professor before moving to NIH, where for several years, she continued her research into the regulation of the p53 tumor suppressor while acting first as Program Director in the Division of Cancer Biology, National Cancer Institute, and later as Program Leader, OSC.

Dana Philpott, Ph.D.

Department of Immunology, University of Toronto

Dr. Philpott is an Associate Professor in the Department of Immunology at the University of Toronto and co-director of the Host-Microbiome Research Network with the support of the Canadian Foundation for Innovation. She obtained her doctoral degree from the University of Toronto, where she studied host-pathogen interactions, focusing on enteropathogenic *Escherichia coli* infection of epithelial cells. Dr. Philpott then completed postdoctoral work at the Institut Pasteur in Paris under the direction of Dr. Philippe Sansonetti and later became a group leader at the Institut. She was recruited to Toronto in 2006. The research focus in Dr. Philpott's laboratory is to understand how Nod-like receptors influence gut homeostasis and how this might impact infection and disease pathogenesis. A particular interest in the laboratory is understanding Crohn's disease pathogenesis by studying the function of genes that have been linked to the development of this disease, including *NOD2* and *ATG16L1,* as well as their interplay with the gut microbiota. Dr. Philpott has over 150 publications, a number of them in high-profile journals. Her discoveries include identification of the peptidoglycan ligands for NOD1 and NOD2 (along with Dr. Gabriel Nunez), uncovering a role for NOD2 and ATG16L1 in bacterial autophagy, and regulation of NOD-driven inflammatory responses by ATG16L1. Dr. Philpott has received a number of awards for research, including the EMBO Young Investigator Award, a Howard Hughes International Scholar award, and the Canadian Association for Gastroenterology Young Investigator Award. Research in the Philpott laboratory is funded by the Canadian Institutes for Health Research, Natural Sciences and Engineering Research Council of Canada and a grant from Crohn's and Colitis Canada/Vertex Pharmaceuticals.

Katherine S. Pollard, Ph.D.

Gladstone Institutes and University of California, San Francisco

Dr. Pollard is a Director and Senior Investigator at the Gladstone Institutes/University of California, San Francisco (UCSF). She received doctoral and master's degrees from the University of California, Berkeley (UCB), Division of Biostatistics under the supervision of Mark van der Laan. Her research at UCB included developing computationally intensive statistical methods for the analysis of microarray data with applications in cancer biology. Dr. Pollard conducted postdoctoral research at UCB with Sandrine Dudoit, followed by a comparative genomics NIH Postdoctoral Fellowship in the labs of David Haussler and Todd Lowe in the Center for Biomolecular Science and Engineering at the University of California, Santa Cruz. She was part of the Chimpanzee Sequencing and Analysis Consortium that published the sequence of the Chimp Genome, and she used this sequence to identify the fastest evolving regions in the human genome. In 2005 Dr. Pollard joined the faculty at the University of California, Davis, Genome Center and Department of Statistics. She moved to Gladstone/UCSF in fall 2008, where she directs an innovation hub that focuses on emerging technologies and informatics.

John F. Rawls, Ph.D.

Department of Molecular Genetics and Microbiology, Center for the Genomics of Microbial Systems, Duke University School of Medicine

Dr. Rawls is Associate Professor in the Department of Molecular Genetics and Microbiology, Duke University, where he uses multiple complementary approaches to understand how host-microbe interactions in the intestine regulate digestive physiology and energy balance. Using gnotobiotic, genetic, genomic, and in vivo imaging approaches, he examines how commensal microorganisms interact with vertebrate hosts to regulate their nutrition and immunity as well as the mechanisms underlying assembly of intestinal microbial communities. Dr. Rawls pioneered the use of gnotobiotic zebrafish to investigate the role of microorganisms in vertebrate biology and uses zebrafish and mice to investigate the bacterial signals and responsive host pathways that regulate host immunity, nutrition, and gene expression. He also uses the zebrafish system to investigate mechanisms underlying the formation and function of adipose tissues having established methods for in vivo imaging of zebrafish adipose tissues to explore the developmental and environmental processes regulating their growth and physiology. Dr. Rawls' complementary use of zebrafish and mice models key aspects of human physiology and pathophysiology to gain new insights into underlying mechanisms. He received his bachelor's degree in biology from Emory University and his doctoral degree in developmental biology from Washington University, St. Louis followed there by postdoctoral work in gastroenterology and microbiology.

Forest Rohwer, Ph.D.

Department of Biology, San Diego State University

Dr. Rohwer is a Professor in the Department of Biology at San Diego State University. He pioneered the use of metagenomics to characterize microbial ecology in coral reefs to investigate the role of microbes and viruses in coral reef health and disease. In addition, Dr. Rohwer's lab is investigating the dynamics of bacteria, phage, and eukaryotic viruses using microbial transcriptomics and viral metagenomics in the respiratory tracts of individuals with and without cystic fibrosis. For his scientific contributions, he has received numerous awards, including the prestigious Young Investigators Award of the International Society of Microbial Ecology and the Marine Microbiology Initiative Investigator Award from the Gordon and Betty Moore Foundation. Dr. Rohwer received his bachelor's degree in biology, chemistry, and history from the College of Idaho and his doctoral degree in molecular biology from the Joint Doctoral Program at the University of California, San Diego, and San Diego State University. After performing postdoctoral training with Dr. Farooq Azam at the Scripps Institution of Oceanography, he became Adjunct Assistant Professor at San Diego State University, rising to the rank of professor there.

Nita H. Salzman, M.D., Ph.D.

Departments of Pediatrics, Microbiology, and Immunology, Medical College of Wisconsin

Dr. Salzman is a Professor of Pediatrics, Microbiology, and Immunology at the Medical College of Wisconsin (MCW). She is also Director of the MCW Center for Microbiome Research, Associate Director of the Medical Scientist Training Program, the CRI Research Unit Leader for the Infection, Inflammation, and Immunology Research Unit; and Director of the GI Clinical Laboratory. Dr. Salzman received her M.D. and doctoral degrees from the New York University School of Medicine. Her pharmacology research focuses on antimicrobial peptides, host-microbe interactions in the GI tract, and microbiota in health and disease. The Salzman laboratory studies innate host defense at mucosal surfaces, focusing on interactions between the mucosal innate immune system, enteric pathogens, and the microbiome, with a dual focus on both basic and translational research.

Cynthia L. Sears, Ph.D.

Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University School of Medicine

Dr. Sears is a Professor of Medicine at John Hopkins University School of Medicine (JHU-SOM). She also has a joint appointment in oncology in the Molecular Microbiology and Immunology Department (Bloomberg School of Public Health) and is a member of the Sidney Kimmel Comprehensive Cancer Center. Her laboratory focuses on studies to determine how the microbiota contributes to colorectal cancer and studies in detail the carcinogenic bacterium and enterotoxigenic *Bacteroides fragilis* (ETBF), which the lab uses as a model for inducing colon inflammation and carcinogenesis. Dr. Sears' lab pioneered in establishing the importance of Th17/IL-17 mechanisms in many cancers, including human colon cancer. More recently her work has focused on identifying bacterial contributions to human colon cancer, hypothesizing that biofilm-associated colon mucosal procarcinogenesis marks an early event in the biology of colonic epithelial cell transformation in a subset of colon cancers, and is testing this hypothesis in both human (2000-person prospective colonoscopy study) and germ-free experimental studies. Recently, the Sears laboratory has initiated work to study the relationship of the microbiome and cardiovascular disease in HIV-infected and HIV-uninfected populations.

Michael P. Snyder, Ph.D.

Department of Genetics and Center of Genomics and Personalized Medicine, Stanford University School of Medicine

Dr. Snyder is the Stanford Ascherman Professor and Chair of Genetics and the Director of the Center of Genomics and Personalized Medicine. Dr. Snyder received his doctoral degree at the California Institute of Technology and carried out postdoctoral training at Stanford University. He is a leader in the field of functional genomics and proteomics and one of the major participants of the ENCODE project. Dr. Snyder's laboratory was the first to perform a large-scale functional genomics project in any organism and has developed many technologies in genomics and proteomics. These include the development of proteome chips, high-resolution tiling arrays for the entire human genome, methods for global mapping of transcription factor binding sites (ChIP-chip now replaced by ChIP-seq), paired end sequencing for mapping of structural variation in eukaryotes, and de novo genome sequencing of genomes using high-throughput technologies and RNA-Seq. These technologies have been used for characterizing genomes, proteomes, and regulatory networks. Seminal findings from Dr. Snyder's laboratory include the discovery that much more of the human genome is transcribed and contains more regulatory information than was previously appreciated and that a high diversity of transcription factor binding occurs both between and within species. He has also combined various state-of-the-art "'omics" technologies to perform the first longitudinal detailed integrative personal 'omics profile (iPOP) of a person and used this to assess disease risk and monitor disease states for personalized medicine. He is a cofounder of several biotechnology companies, including Protometrix (now part of Life Technologies), Affomix (now part of Illumina), Excelix, and Personalis, and he serves on the boards of directors of several companies.

Justin Sonnenburg, Ph.D.

Department of Microbiology and Immunology, Stanford University School of Medicine

Dr. Sonnenburg is an Associate Professor in the Department of Microbiology and Immunology at the Stanford University School of Medicine, where he studies the gut microbiota in health and disease and co-directs the Center for Human Microbiome Studies. His laboratory at Stanford focuses on understanding basic principles that govern interactions within the intestinal microbiota and between the microbiota and the host. An ongoing objective of the research program is to devise and implement strategies to prevent and treat disease in humans via the gut microbiota. Dr. Sonnenburg and his wife Erica wrote the book The Good Gut: Taking Control of Your Weight, Your Mood, and Your Long-Term Health.

Thaddeus Stappenbeck, M.D., Ph.D.

Department of Pathology and Immunology, Washington University School of Medicine, St. Louis

Dr. Stappenbeck is the Conan Professor of Pathology and Immunology at the School of Medicine at Washington University, St. Louis (WUSL). He also serves as Co-Chief of his Department's Division of Laboratory and Genomic Medicine and directs the WUSL Histology and Microscopy Core in the Department of Developmental Biology. A major focus of Dr. Stappenbeck's research has been host-microbial interactions. Notably, his laboratory has collaborated with others to develop and characterize novel mouse models that have mutations in genes that lead to inflammatory phenotypes. They also have determined how host mutations influence interactions with the environment (i.e., specific microbes) to alter function and inflammation. Dr. Stappenbeck's lab has extensive expertise in the analysis of inflammatory intestinal phenotypes in mice and has also developed novel in vitro systems of intestinal epithelial culture that used by other investigators to address novel microbiome questions. Some of his key contributions have been (1) defining a role for autophagy proteins in the GI epithelium, (2) defining the role of lamina propria cells in injury repair, (3) minimal reporting of best practices for animal husbandry fin microbiome studies, and (4) defining novel roles of bacterial and viral infection in injury generation and repair.

Michiko E. Taga, Ph.D.

Department of Plant and Microbial Biology, University of California, Berkeley

Dr. Taga is an Associate Professor in the Department of Plant and Microbial Biology at the University of California, Berkeley. Her research interests focus on understanding how microorganisms that reside in complex communities interact through the sharing of nutrients and how these interactions shape the composition and function of microbial communities. Her major research focus is on the vitamin B12 family of molecules (corrinoids), nutrients that are synthesized only by a fraction of the bacteria that use them. Dr. Taga's lab uses molecular biology, genetics, biochemistry, and analytical chemistry to investigate how these cofactors are synthesized, used, and acquired by bacteria. She received her bachelor's degree in biology from Carleton College and her doctoral degree in molecular biology from Princeton University, where she investigated the function of the quorum-sensing autoinducer AI-2 in the laboratory of Bonnie Bassler. Dr. Taga performed postdoctoral research on bacteria-host interactions and vitamin B12 biosynthesis in the laboratory of Graham Walker at the Massachusetts Institute of Technology and has been an Assistant Professor at the University of California, Berkeley, since 2009.

Peter J. Turnbaugh, Ph.D.

Department of Microbiology and Immunology, University of California, San Francisco

You are not alone: Each human being is home to trillions of microbes that have a widespread impact on human physiology and predisposition to disease. Dr. Turnbaugh's laboratory studies the role of these microbes in two major areas, pharmacology and nutrition, with a current focus on the role of gut microbial metabolism in influencing the predisposition to and treatment of heart disease, cancer, and autoimmune disease. The lab's main two experimental approaches are gnotobiotics (germ-free and colonized mice) and metagenomics (culture-independent methods for studying microbial communities). The lab members collaborate closely with other members of the rich University of California, San Francisco, microbiome community, including Michael Fischbach, Susan Lynch, and Katie Pollard. The

Turnbaugh lab's primary thematic area is virology and microbial pathogenesis. Its secondary thematic area is immunology. Both areas focus on the impact of the human gut microbiome on pharmacology and nutrition.

Harris H. Wang, Ph.D.

Department of Systems Biology, Columbia University

Dr. Wang is an Assistant Professor in the Department of Systems Biology at Columbia University , where his long-term goal is to delineate and understand the genetic, metabolic, and host factors that enable the spatiotemporal microbial colonization of the gastrointestinal tract during healthy and dysbiotic states. He has developed advanced strategies to manipulate the gut microbiota in situ using synthetic biology approaches. Building on previous work where Dr. Wang developed high-efficiency genome engineering tools for both bacteria and eukaryotic systems, he examines metabolic cross-feeding dynamics in complex microbial consortia. He is using a new technique to identify carbohydrate utilization genes that are key to sustained survival in the gut. He received his bachelor's degree in physics and mathematics from the Massachusetts Institute of Technology (MIT) and his doctoral degree in medical engineering and medical physics through a joint MIT-Harvard University program. Notable honors include the 2017 PECASE award, 2017 Burroughs Wellcome Fund PATH, award and an NIH Director's Early Independence Award.

Owen R. White, Ph.D.

Institute for Genome Sciences, University of Maryland School of Medicine

Dr. White is a Professor of Epidemiology and Public Health and Associate Director of Informatics at the Institute for Genome Sciences (IGS) at the University of Maryland School of Medicine. He is also Co-Director of the Center for Health-Related Informatics and Bioimaging (CHIB). Dr. White and the IGS Bioinformatics Department are involved in large-scale annotation, ontology development, and data sharing. He has overseen the annotation of hundreds of genomes sequenced using computer analyses in combination with systematic manual evaluation. Dr. White's group currently runs the integrated Human Microbiome Project's Data Coordination Center. He has been awarded the Benjamin Franklin Award for Open Access in the Life Sciences from The Bioinformatics Organization.

Gary D. Wu, M.D.

University of Pennsylvania School of Medicine'

Dr. Wu is the Ferdinand G. Weisbrod Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania, where he is Associate Chief for Research in the Division of Gastroenterology, Associate Director of the Center for Molecular Studies in Digestive and Liver Disease, and Co-Director of the PennCHOP Microbiome Program. He was the inaugural Director and Chair of the Scientific Advisory Board for the American Gastroenterological Association Center for Gut Microbiome Research and Education and is an elected member of both the American Society for Clinical Investigation and the American Association of Physicians. Research programs in the Wu laboratory focus on the mutualistic interactions between the gut microbiota and its host with a particular emphasis on metabolism, including nitrogen balance, intestinal oxygen regulation, and epithelial intermediary metabolism. Of

particular interest is the effect of diet on the gut microbiome and its relationship to therapeutic responses associated with the use of defined formula diets in the treatment of Crohn's disease. Insights gained from these projects will hopefully lead to the development of better diets for patients with inflammatory bowel disease.

Ramnik Xavier, M.D.

Harvard Medical School and Broad Institute, Harvard University

Dr. Xavier received his M.B. and Ch.B. degrees from the University of Zimbabwe and completed his residency and fellowship at the Massachusetts General Hospital (MGH). He is a member of the Broad Institute and Chief of Gastroenterology at MGH, Kurt Isselbacher Professor of Medicine at Harvard Medical School, and Director of MGH's Center for the Study of inflammatory bowel disease (IBD). Dr. Xavier's laboratory uses genetic, structural, computational, and animal models, as well as clinical research to define the mechanisms controlling inflammation and immunity in vivo. Recent findings in the lab have helped elucidate the role of autophagy—a cellular process that digests and recycles proteins—in the development of Crohn's disease. His team has also discovered novel immune regulatory genes involved in innate and adaptive immunity; identified innate immune pathways that sense microbial invaders (danger signals); and pinpointed metabolic stress programs in immunity. In addition, Dr. Xavier and his team are part of the Human Microbiome Project (HMP2) funded by the NIH Common Fund and the Crohn's and Colitis Foundation and are pursuing new methods to understand the relationship between microbes living in the human gut and IBD and to connect these patterns back to human genetics. He also co-directs the Center for Microbiome Informatics and Therapeutics at MIT and leads a program to look for connections between the microbiome and type 1 diabetes. In his role as Chief of Gastroenterology at MGH, which he assumed in 2010, Dr. Xavier oversees one of the only comprehensive, multidisciplinary programs in New England dedicated to diagnosing, treating, and managing patients with Crohn's disease and ulcerative colitis. U.S. News & World Report has ranked the center third in the country for digestive care (number 1 in New England). He was elected to the American Association of Physicians in 2011 and is also a fellow of the American College of Physicians and the American College of Gastroenterology.

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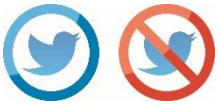

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POSTER TITLES AND NUMBERS

DAY 1			
Poster Number	**Title**	**Presenter**	**Page Number**
1	Host Immune Response Supports Fecal Microbiota Transplant-Mediated Clearance of Clostridium Difficile Infection	Michael C. Abt	69
2	Discovering Differences Between Patient Groups From Metagenomic and Metatranscriptomic Data	Tom Arodz	69
3	Translating Metagenomics by Developing Methods to Measure, Model, and Intervene on the Human Microbiome	Ami S. Bhatt	70
4	Host Genomic Control of the Microbiome in Colorectal Cancer	Ran Blekhman	71
5	A Functional Screen of Crohn's Disease-Associated Microbial Metabolites Identifies Unprecedented Molecules Modifying Mucosal Cell Biology	Yu-Ling Chang	76
6	HuMiX – A New Biomimetic Tool for Organ-on-Chip Models	Carla Brooks	72
8	The Human Virome in Health and Disease	Frederic D. Bushman	72
9	Intranasal Lactobacillus Rhamnosus Attenuates Influenza Infection in the Neonatal Mouse	Alison J. Carey	73
10	Comparisons of the Gut Microbiota of Generally Healthy Black and White Women in the Southern United States	Tiffany L. Carson	74
11	Transcriptomic Profile of the Caenorhabditis Elegans Intestinal Bacteria	Regina Lamendella	100
12	Microbial Modification of Colonic Mucosal Gene Expression Response to a Flaxseed Lignan Extract Intervention in Humans	Robert S. Chapkin	76
13	A Simple Bacterial Consortium Protects Against the Development of Colon Tumors	Grace Y. Chen	77
14	Modeling the Microbiome in Colorectal Cancer: Emerging Approaches to Hypothesis Testing	Nicholas Chia	77
15	Gene-Microbiota Interactions Contribute to the Pathogenesis of Inflammatory Bowel Disease	Hiutung Chu	78
16	Early Life Stress/Pain Experience Imprints Gut Microbiome in Preterm Infants	Xiaomei Cong	78
18	The Gut-Microbiome-Brain Axis in Neurodevelopmental Disorders	Mauro Costa-Mattioli	79
19	Butyrate Protects Gut-Liver Axis During Chronic-Binge Ethanol Exposure	Gail A.M. Cresci	81

DAY 1			
Poster Number	**Title**	**Presenter**	**Page Number**
20	Commensal Composition and Efficacy of Microbiota-Based Treatments Are Influenced by Innate Immunity	R. William DePaolo	81
21	Exploring Bacteriophage Community Composition During Intestinal Colitis	Breck A. Duerkop	82
23	Distinct Microbiota in the Cervicovaginal Space Are Associated With Spontaneous Preterm Birth	Michal A. Elovitz	82
24	Predictors of Preterm Birth in a Longitudinal, Multi-Omic Study of the Vaginal Microbiome	Jennifer M. Fettweis	83
26	Characterizing the Role of Vaginal Veillonellaceae Species in Women's Reproductive Health and Pregnancy	Abigail Glascock	85
27	Changes in the Gut Microbiota by Prenylated Flavonoid Supplementation Are Associated With Improvements in Dysfunctional Glucose and Lipid Metabolism in Mice Fed a High-Fat Diet	Adrian F. Gombart	85
28	The Preterm Infant Microbiome: Growth, Health, and Development at 2 and 4 Years of Age	Maureen Groer	86
29	Associations Between Vaginal Microbiota and Genitourinary Symptoms of Menopause	David N. Fredricks	84
30	Omega-3 Fatty Acids Protect Murine Fetuses From Bacteria-Induced Placental Inflammation Originating From Maternal Endothelial Cells	Yiping W. Han	86
31	Early Life Colonization of the Nasopharyngeal Microbiome: A Longitudinal Study in The Gambia	Blake M. Hanson	87
32	Development of New Genetic Tools to Determine the Role of Siderophores in Clostridium Difficile Pathogenesis	Jessica L. Hastie	87
33	Fecal Bile Acids and Steroids Correlate With Abdominal Pain in Children With Irritable Bowel Syndrome	Emily B. Hollister	90
34	Functional Dynamics of the Gut Microbiome in Healthy Subjects During and After 6 Months of Consumption of Probiotic Lactobacillus Rhamnosus GG ATCC 53103 vs. Placebo	Patricia L. Hibberd	88
35	Modulation of Neointimal Hyperplasia Severity in Rats by Commensal Microbial Transfer	Karen J. Ho	88
36	Metabolomic Profiling of the Infant Stool Microbiota: Associations With Delivery Mode and Diet in the New Hampshire Birth Cohort Study Metabolomic Profiling of the Infant Stool Microbiota	Anne G. Hoen	89
37	Host-Bacteria Genome Interactions in Tumors	Julie C. Dunning Hotopp	91

DAY 1			
Poster Number	**Title**	**Presenter**	**Page Number**
38	Analysis of the Vaginal Microbiome in Health and Disease	Bernice Huang	91
39	Synergy Between Genes and the Environment: The Effect of the Microbiome and Host Genetic Variation on Exposures to Enterolignans and Steroid Hormones in Post-Menopausal European American and African American Women	Meredith A.J. Hullar	92
40	Commensal Mucin Degradation Stimulates Respiratory Pathogen Growth in Chronic Lower Airway Disease	Ryan Hunter	92

DAY 2			
Poster Number	**Title**	**Presenter**	**Page Number**
1	Gut Microbiome Metagenome and Metatranscriptome in the Context of Colorectal Carcinogenesis Studies	Andrew T. Chan	75
2	Intestinal Microbiota Influence Thymic Development in Neonates	Nitya Jain	93
3	HIV Exposure and Gut Microbiota in South African Infants	Heather Jaspan	93
4	Analysis of Niche-Specific Adaptations of Vaginal Bifidobacterium spp. Leveraged by Longitudinal Datasets	Nicole R. Jimenez	94
5	Human Derived Gut Microbiota Modulates Colonic Secretion in Mice by Regulating 5-HT3 Receptor Expression via Production of Acetate	Purna C. Kashyap	94
6	Airway Colonization Induces Th17 Responses in the Lungs and Modulates Allergic Airway Sensitization in Mouse Model of Asthma	Andrew Kau	95
7	Microbial Delivery of Antimicrobial Peptides for Protection Against Multidrug-Resistant Pathogens	Yiannis Kaznessis	95
8	Nasal Microbiome Features of Staphylococcus Aureus Colonization and Infection During Critical Illness	Brendan J. Kelly	96
9	Gut Microbial Metabolites Fuel Host Antibody Responses	Chang Kim	96
10	Probiotic Use of Women Followed for Gut Microbial Composition in Relation to Perinatal Mood and Anxiety Disorders	Mary Kimmel	97
11	Vaginal Bacteria Modify HIV Tenofovir Microbicide Efficacy in African Women	Nichole R. Klatt	97
12	Exposure to Luminal Antigens in Early Life Is Controlled for the Promotion of Tolerance to the Microbiota	Kathryn A. Knoop	98
13	Roux-en-Y Gastric Bypass Surgery Shifts Gut Microbial Communities and Associated Metabolites	Rosa Krajmalnik-Brown	99
14	Lactobacillus-Deficient Cervicovaginal Bacterial Communities Are Associated With Increased HIV Acquisition in Young South African Women	Douglas Kwon	99
15	Gut Microbial Dysbiosis and Post-Transplant Complications in Kidney Transplant Recipients	John Lee	100
17	Dissecting the Human Skin Microbiome in Health and Disease – From Strain-Level Composition to Transcriptional and Metabolic Activities in the Host Environment	Huiying Li	101

DAY 2			
Poster Number	**Title**	**Presenter**	**Page Number**
18	Role of the Human Virome in Kidney Transplant Disease	Efrem Lim	102
19	Resetting Gut Microbiota by Lactobacillus Reuteri DSM 17938 Inhibits Treg-Deficiency-Induced Autoimmunity (IPEX Syndrome) Via Adenosine 2A Receptors	Yuying Liu	102
20	Niche-Association and Retention Dynamics in the Human Microbiome	Jason Lloyd-Price	103
21	The Critical Window in Neonatal Microbiome Development: Exposures and Outcomes	Juliette C. Madan	104
22	Composition of Vaginal Microbiota During Labor and the Effect of Lubricant Use	Katie G. McElroy	104
23	Gut Microbiota and Cardiovascular Disease (CVD) Risk Factors: Early Results from the CARDIA (Coronary Artery Risk Development in Young Adults) Microbiome Study	Katie A. Meyer	105
24	Fecal Microbiota Transplantation in Children Does not Significantly Alter Body Mass Index	Sonia Michail	106
25	Maternal High-Fat Diet Results in Microbiota-Dependent Expansion of Type 3 Innate Lymphoid Cells (ILC3s) and Susceptibility to Inflammation in Neonatal Mice	Julie Mirpuri	106
26	Effects of Infant Diet on the Developing Gut Resistome	Aimee Moore	107
27	High Pulmonary Arterial Pressures Are Associated With Decreased Oral Microbial Nitrate Metabolism in the Mouth	Alison Morris	107
28	Control of Epithelial Homeostasis by the Microbiota	Andrew Neish	108
29	Control of Pathogen Colonization by Host Immunity and the Microbiota in the Gut	Gabriel Nuñez	108
30	Tumor Necrosis Factor Receptor 2 Restricts Dysbiosis in Colitis	D. Brent Polk	109
31	Circulating Microbiome and Functional Metagenomic Signature Is Associated With Heavy Alcohol Use and Severity of Alcoholic Hepatitis	Puneet Puri	109
32	The Role of Gut Microbiota in Chemotherapy-Induced Behavioral Comorbidities	Leah M. Pyter	110
33	Gut Microbiota, Tryptophan Catabolism, and Atherosclerosis in HIV Infection	Qibin Qi	110
34	TAS2R38 Genotype-Associated Alterations in Sinus Microbiota	Vijay R. Ramakrishnan	111
35	New Insights to the Role of Lactic Acid on the Vaginal Host-Microbe Interaction	Jacques Ravel	111

DAY 2			
Poster Number	**Title**	**Presenter**	**Page Number**
36	Therapeutic Targeting of the Gut Microbiota	Matthew R. Redinbo	112
37	Longitudinal Dynamics of the Vaginal and Fecal Microbiota During Pregnancy and Gestation at the Onset of Labor	Mary Regan	112
38	Bile Acid C12-hydroxy Epimerization by Human Gut Microbiota	Jason M. Ridlon	113
39	Grape Proanthocyanidin-Induced Bloom of Gut Microbe Akkermansia Muciniphila Precedes Intestinal Gene Expression Changes Associated With Metabolic Resilience	Diana E. Roopchand	114
40	The Microbial Metabolome: The Missing Link Between Diet and Human Health	Wendy Russell	114

DAY 3			
Poster Number	**Title**	**Presenter**	**Page Number**
1	Characterization of Fecal Microbiota in Response to Heterologous Versus Autologous Fecal Microbial Transplantation	Michael J. Sadowsky	115
2	Dynamic Longitudinal Transcriptome Differences Across Healthy and Respiratory Viral Infections and Between Pre-Diabetic and Non-Diabetic States	M. Reza Sailani	115
3	Early Microbial Antigen Priming Sets the Course for Host Immune Tolerance vs. Immunity	Tiffany C. Scharschmidt	116
4	Temporal Dynamics of Metatranscription in Inflammatory Bowel Disease	Melanie Schirmer	116
5	The Effects of Phage Therapy Against Vancomycin-Resistant Enterococci and the Gut Microbiota	Paul E. Carlson, Jr.	73
6	Unraveling the Microbiome of Primary Immune-Deficient Patients	Julia A. Segre	117
7	Multi-Omic Microbiome Study-Pregnancy Initiative (MOMS-PI)	Myrna G. Serrano	117
8	A Protective Major Histocompatibility Complex-Class II Allele Prevents Autoimmune Diabetes by Shaping the Intestinal Microbiome Early in Ontogeny	Michael A. Silverman	118
9	The Impact of Sex, Age, and Diet on the Microbiome and Metabolome	Carolyn Slupsky	118
10	MAIT Cells: Shaping the Microbiome and Contributing to Clostridium Difficile Infection	Paul E. Carlson, Jr.	74
11	Regulation of Host-Microbiota Relationships in Human Health and Disease	Gregory F. Sonnenberg	119
12	Akkermansia Muciniphila May Be Permissive to Arthritis in the K/BxN Mouse Model of Arthritis	Matthew Stoll	119
13	A Disease-Protective Human Commensal Discovered Using Microbial Pedigree Analysis	Neeraj K. Surana	120
14	The Interplay Between Gut Microbiota-Derived Secondary Bile Acids and C. Difficile Pathogen Dynamics	Casey M. Theriot	121
15	Clostridiales Correlate With Intestinal Barrier Maturation in Preterm Infants	Bing Ma	103
16	Strain-Level Identification of Mother-to-Child Bacterial Transmission During the First Few Months of Life	Hera Vlamakis	121
17	The Human Gut Microbiome Protects Against Arsenic Toxicity	Seth T. Walk	122
18	The Importance of Colonization History in Gut Microbiota Assembly	Jens Walter	122

DAY 3			
Poster Number	**Title**	**Presenter**	**Page Number**
19	Microbe-Mitochondria Interaction in Host Longevity Regulation	Meng Wang	123
20	Vibrio Cholerae Infection and the Duodenal Microbiome	Ana Weil	123
21	Antibiotic-Induced Microbiome Depletion Alters Glucose Homeostasis by Affecting Intestinal Signaling and Colonic Energy Metabolism	Amir Zarrinpar	124
22	Antibiotics Disrupt Gastrointestinal Microbiota and Mucosal Immunity in Rhesus Macaques	Alexander S. Zevin	124
23	Integrative Personal Omics Profiles During Periods of Weight Gain and Loss	Wenyu Zhou	125
24	Effects of Intermittent Fasting on the Gut Microbiome in Multiple Sclerosis	Yanjiao Zhou	125
25	Dynamics of the Oral, Vaginal, and Gut Microbiome of African American Women With Full-Term Pregnancies	Elizabeth J. Corwin	79
26	Impact of Resistant Starch on the Human Gut Microbiome	Colin J. Brislawn	71
27	Commensal Corynebacterium Shifts Staphylococcus Aureus Toward Commensalism by Quenching Quorum Sensing	Katherine P. Lemon	101
28	Open Science Data Framework	Victor Felix	83
29	Characterization of the Stool Metabolome to Study Associations with the Gut Microbiome and Inflammatory Bowel Disease (IBD)	Julian Avila-Pacheco	70
30	Human Microbiome Project Data Resources	Heather Huot Creasy	80
31	HMP DACC Data Portal	Jonathan Crabtree	80
32	Metabolic Modeling of the Vaginal Microbiome: Methods and Progress Updates	Eunsoo Hong	90

Host Immune Response Supports Fecal Microbiota Transplant-Mediated Clearance of Clostridium Difficile Infection

Michael C. Abt, Rebecca A. Carter, Eric R. Littmann, Boj Susac, Lilian Lang, Eric G. Pamer

Memorial Sloan Kettering Cancer Center

Clostridium difficile is an opportunistic pathogen that infects the large intestine following perturbation of the intestinal microbiota causing epithelial damage and debilitating, potentially fatal, colitis. Current antibiotic treatment options result in high recurrence rates, highlighting the need to identify alternative approaches to control this disease. Fecal microbiota transplantation (FMT) is clinically proven to efficiently clear recurrent C. difficile infection. Despite remarkable efficacy, implementation of FMT therapy is limited due to inadequate understanding of FMT mechanism of action. Here, we use a murine model of chronic C. difficile infection to demonstrate a critical role for the host's immune system in determining efficacy of FMT. C57BL/6 and T & B cell deficient Rag1-/- mice were infected with C. difficile and exhibited comparable establishment of chronic infection with no difference in bacterial burden or toxin levels in the colon. Following FMT, chronically infected C57BL/6 mice resolved C. difficile infection within two weeks while cohoused Rag1-/- mice failed to clear the infection. FMT in chronically C. difficile infected mice that lack B cells, CD8+ T cells or CD4+ T cells revealed a necessary role for CD4+ T cells, but not B cells or CD8+ T cells, in resolution of C. difficile following FMT. Analysis of intestinal bacterial communities following FMT demonstrate the microbiota of C57BL/6 mice assimilated toward the composition of the FMT donor, while the intestinal microbiota of Rag1-/- and CD4+ T cell deficient mice did not acquire the bacterial composition of the FMT donor. These data suggest that FMT engraftment and efficacy is dependent on an intact CD4+ T cell compartment.

Discovering Differences Between Patient Groups From Metagenomic and Metatranscriptomic Data

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Virginia Commonwealth University

We present a pipeline for machine learning-based discriminative modeling between patient groups using annotated metagenomic and metatranscriptomic patient data. Currently, the approaches for discovering differences between clinically or demographically-defined patient groups rely either on bacterial composition obtained from 16S sequencing, or on annotation of individual genes or pre-defined pathways in their metagenomic or metatrascriptomic data. The proposed pipeline uses discriminative linear classification model expanded to include a graph regularization term, which allows for using existing knowledge of interactions among genes as a biological-based regularizer that improves the robustness of the model. As a validation, we have used the proposed technique on vaginal microbiome samples, but the method is applicable to other microbiome datasets.

Characterization of the Stool Metabolome to Study Associations with the Gut Microbiome and Inflammatory Bowel Disease (IBD)

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Broad Institute, Harvard University

A number of factors contribute to the complex array of small molecules that occur in stool; including diet, gut flora, and gut function. Comprehensive profiling of the stool metabolome therefore can provide detailed phenotypic information on health status, metabolic interactions between the host and the microbiome, and interactions among gut microbes. Here, we applied metabolomics on stool samples collected longitudinally from inflammatory bowel disease (IBD) patients and non-IBD controls who participated in the Integrative Human Microbiome Project (iHMP). A total of 546 samples were analyzed using a platform comprised of four complementary liquid chromatography tandem mass spectrometry (LC-MS) methods designed to measure polar metabolites and lipids. Each method used high resolution/accurate mass (HRAM) profiling to measure both metabolites of confirmed identity and yet to be identified metabolite peaks. 81,867 de-isotoped LC-MS peaks were measured, out of which 597 were annotated based on confirmation with authentic reference standards. Pooled stool extracts inserted and analyzed throughout the analysis queues to evaluate analytical reproducibility showed a median coefficient of variation of 5.1% among known metabolites and 24.2% across all 81,867 features. Owing to differences in water content and heterogeneity among stool samples, we evaluated different scaling methods to standardize the metabolomics data. Finally, a series of univariate and multivariate statistical analyses were conducted to detect features that discriminate IBD from controls in adults and children. These metabolomics data will be incorporated into a multi'omic database that will enable the study of associations between the gut microbiome and IBD.

Translating Metagenomics by Developing Methods to Measure, Model, and Intervene on the Human Microbiome

Ami S. Bhatt

Stanford University

Our group hopes to understand how microbes and microbial products impact host cell biology and subsequently host disease phenotypes. We iteratively develop and apply tools to measure relevant features of the microbes (beyond taxonomy) and the host response, model these interactions/relationships, and then intervene to directly target the microbiome or its products with the intention of improving host health. We focus on two study populations: (1) heavily immunocompromised patients, and (2) rural and urban underserved African patients either with or at high risk of developing noncommunicable diseases. Specifically, we are measuring the impact of antibiotic and chemotherapeutic exposure on the host microbiome, and in particular, are interested in modeling microbial genomic plasticity that may be induced by drug exposure. In order to test the hypothesis that these exposures drive genomic instability in microbial populations, perhaps through the activation of transposable sequences, we have used a series of patient stool samples taken from patients undergoing hematopoietic cell transplantation. By applying the 10X read cloud sequencing technology and a custom bioinformatic pipeline, we have identified that the microbe in which transposition appears to be most active is also the one that ends up dominating the gut microbiome of this individual. This finding suggests that transposition may be an adaptive stress-response mechanism.

Lastly, we are also investigating a novel prebiotic approach (phase I clinical trial) to intervene and modify the microbiome in an attempt to improve outcomes in HCT patients.

Host Genomic Control of the Microbiome in Colorectal Cancer

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University of Minnesota

Variation in the gut microbiome has been linked to colorectal cancer (CRC), as well as to host genetic variation. However, we do not know whether, in addition to baseline host genetics, specific somatic mutations in CRC tumors interact with the surrounding tumor microbiome, and if so, whether these changes can be used to understand microbe-gene/pathway interactions with potential functional biological relevance. Here, we characterized the association between CRC microbial communities and tumor mutations using microbiome profiling and whole-exome sequencing in tumors and matched normal tissues. We found statistically significant associations between mutations in tumor genes and shifts in the abundances of specific sets of bacterial taxa, suggestive of potential functional interaction. This correlation allows us to statistically predict the existence of loss-of-function tumor mutations in cancer-related genes, such as APC, as well as in relevant pathways, including MAPK signaling pathway, Wnt signaling pathway, and direct P53 effectors, solely based on the composition of the microbiome. These results can serve as a starting point for fine-grained exploration of the functional interactions between discrete alterations in the tumor and proximal microbial communities in CRC. In addition, this work has the potential to lead to the development of microbiome-based CRC screening methods, as well as individualized microbiota-targeting therapies.

Impact of Resistant Starch on the Human Gut Microbiome

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Diet can influence the composition of the human microbiome, yet relatively few dietary ingredients have been systematically investigated with respect to their impact on the functional potential of the microbiome. Dietary resistant starch (RS) has been shown to have health benefits, but we lack a mechanistic understanding of the metabolic processes that occur in the gut during digestion of RS. Here we collected samples during a dietary crossover study with diets containing high or low amounts of RS. We determined the impact of RS on the gut microbiome and metabolic pathways in the gut, using a combination of 'omics' approaches, including sequencing, metaproteomics and metabolomics. This multi-omics approach captured changes in the abundance of specific bacterial species, proteins and metabolites after a diet high in resistant starch (HRS), providing key insights into the influence of dietary interventions on the gut microbiome. The combined data showed that a high RS diet caused an increase

in the ratio of Firmicutes to Bacteroidetes, including increases in relative abundances of several members of the Firmicutes, and concurrent increases in enzymatic pathways and metabolites involved in lipid metabolism in the gut.

HuMiX – A New Biomimetic Tool for Organ-on-Chip Models

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The etiology of certain idiopathic medical conditions, e.g., cardiovascular diseases, diabetes or Parkinson's disease, has recently been linked to human gastrointestinal microbiota. However, the underlying molecular and ecological processes/mechanisms that determine microbial and human cellular transitions between both health and disease states are still unclear. At present causative links are difficult to ascertain due to a distinct lack of in vitro human-microbial co-culture systems in which emergent hypotheses can be tested.

Here, our team will present the design, fabrication and development of a microfluidic-based in vitro co-culture device (HuMiX), allowing co-cultivation of human and microbial cells. The modular device architecture provides access to individual co-cultured contingents following targeted perturbations, which facilitate high-resolution systemic investigations into the hypothesized role of the complex host-microbial molecular interactions in the pathogenesis of idiopathic medical conditions and insight into the functional attributes of microbiomes in the broader context of microbial systems ecology.

We will also report data on the characterization of this co-culture system with module-by-module approach, focusing on evaluation of the optimal conditions for human intestinal epithelial cell culture in the device and anaerobic conditions in the gut microbial culture compartment. We will present work on the design and prototyping of the system and discuss a future configuration of the HuMiX platform for exploring the microbiome gut-brain axis model.

The Human Virome in Health and Disease

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Humans harbor enormous communities of viruses that are important in health and disease. Transient viral infections are well known to most people, but this is just the tip of the iceberg. The human genome is composed of some 8% viral sequences, and the gut microbiome contains viruses in enormous numbers, comparable to bacteria. Viruses can cause disease directly, but they also modulate the composition of the microbiome in health. Many viral groups are poorly represented in genome databases, so that specialized methods must be used to study them. Metagenomic methods, however, allow these viral communities to be tracked, permitting longitudinal quantification, analysis of variation over time, and tracking transfer of viral communities during transplantation between human individuals. Results from recent experiments on the human virome will be presented.

Intranasal Lactobacillus Rhamnosus Attenuates Influenza Infection in the Neonatal Mouse

Alison J. Carey, Ogan K. Kumova, Adam J. Fike, Jillian L. Thayer, Judith Pascasio, Jennifer L. Hope, Linda Nguyen, Christopher Stairiker, Peter D. Katsikis

Drexel University College of Medicine

Investigations into the use of probiotics for respiratory infections in infants are lacking. Intranasal administration of Lactobacillus rhamnosus (LGG) to adult mice significantly reduced symptoms and increased survival rates in Influenza-infected mice. Therefore, we sought to determine if intranasal administration of a probiotic prior to influenza infection would protect neonatal mice. We developed a model where three-day old neonatal C57Bl/6 mice were infected intranasally with PR8 influenza virus. Neonatal mice were given 1x106 live colony forming units of LGG or sham intranasally on days 1 and 2 of life. All mice were infected on day of life 3 with PR8 influenza. Animals were harvested at Day 3 and 6 post-infection and lungs and spleens were analyzed for lymphocyte sub-populations by flow cytometry. Viral loads and cytokines were determined by real time PCR. Cell counts and viral loads were normalized per 100 mg of lung tissue. LGG pretreated mice had a much improved survival rate as compared to the neonates given sham (60% versus 10%, $p<0.001$). The infection is attenuated, as shown by a reduction in viral loads on day 3 post-infection in the LGG pre-treated group as compared to control neonates ($p<0.03$). In addition, IFN gamma expression is reduced 3 fold in those animals pretreated with LGG ($p<0.03$), as compared to control neonates. Viral loads by day 6 are similar between the 2 groups. At day 3 post-infection, there is an influx of CD8+ T cells in the lungs of LGG pretreated mice (12.6% ± 1.0 versus 3.8% ± 0.4, $p=0.01$). These studies indicate that the use of probiotics can attenuate the morbidity and mortality associated with respiratory infections in a neonatal animal model.

The Effects of Phage Therapy Against Vancomycin-Resistant Enterococci and the Gut Microbiota

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Antibiotics have saved millions of people from diseases such as pneumonias, healthcare associated infections, and foodborne illnesses. However, the continued use of antibiotics has led to several unintended consequences, including disruption of the indigenous gut bacteria and a rise in antibiotic-resistant bacteria. Vancomycin-resistant enterococci (VRE), which have been classified as a serious threat by the Centers for Disease Control and Prevention, are responsible for 20,000 U.S. infections annually. The inability to treat these infections with common antibiotics necessitates the development of alternative methods of intervention. The objective of my investigation is to develop and characterize an effective bacteriophage therapy against VRE. To that end, several naturally occurring phage isolates with activity against a range of VRE strains were isolated from sewage. I have administered antibiotics in mice to disrupt the normal gut microbiota and allow VRE to colonize and persist. Using virulent phages, I designed a cocktail with high activity against the E. faecalis strain used to infect mice. This cocktail and an individual phage were administered to VRE colonized mice to study their efficacy. Preliminary data suggests that phage could be successfully utilized to decolonize VRE infected mice. These treatments are being compared to a standard antibiotic intervention, ampicillin, for differences in efficacy as well as their effects on the microbiota. We hypothesize that bacteriophage therapy will have minimal effects on the microbiota compared with antibiotic treatment. These bacteriophage therapy investigations will

have a significant impact on a largely understudied field and contribute to solving the antibiotic-resistant bacteria problem.

MAIT Cells: Shaping the Microbiome and Contributing to Clostridium Difficile Infection

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Clostridium difficile (Cd) is a leading cause of nosocomial infection. Cd infection (CDI) typically occurs following antibiotic usage, which perturbs the gut microbiota leaving the host susceptible to Cd colonization. Mucosa-associated invariant T cells (MAIT) cells recognize intermediates of riboflavin biosynthesis presented on MR1, an MHC-I like related molecule. MAIT cell development is dependent on the host microbiome. MAIT cells are found in high numbers at mucosal sites and are beneficial in combatting various pulmonary infections; however their role in gut infections is unknown. We hypothesized that MAIT cells would play a role in controlling CDI. To test this hypothesis, WT and MR1-/- (lacking MAIT cells) mice were treated with antibiotics and then infected with Cd spores. Stool was collected for 16S rRNA sequencing and plated to determine Cd colonization levels for several days post-infection. Contrary to our hypothesis, MR1-/- mice showed no signs of disease or detectable levels of Cd colonization. A more pathogenic strain of Cd was also tested and MR1-/- mice remained resistant. Fecal microbiota transplantation (FMT) was conducted to determine the role of the microbiota in this resistance phenotype. Susceptible WT mice given FMT from MR1-/- mice experienced dramatically lower colonization levels by day 7 and cleared detectable Cd by day 14, while WT mice given control FMT continued to exhibit high colonization levels. 16S rRNA sequencing of fecal samples from each strain revealed inherent phylum level differences in relative abundance of Bacteroidetes, Firmicutes, and Verrucomicrobia after antibiotics and FMT. Our data suggest the MR1-/- gut microbiome is resistant to Cd colonization, and this resistance is transferrable via FMT.

Comparisons of the Gut Microbiota of Generally Healthy Black and White Women in the Southern United States

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Racial health disparities persist among black and white women for many chronic health conditions. The purpose of this study was to compare the gut microbiota of generally healthy black and white women and to explore whether perceived psychological stress contributed to any observed differences. Generally healthy volunteers > 19 years old and self-identified as non-Hispanic black or white were recruited. Exclusion criteria were (1) current tobacco use, (2) current pregnancy, (3) prior cancer diagnosis, or 4) use of antibiotics in the previous 90 days. Participants provided demographics, anthropometric, and survey data. Stool samples were also collected using a standardized protocol. Fecal

DNA was isolated and PCR was used to amplify the V4 region of the 16SrRNA gene and sequenced using the MiSeq platform. Microbiome data was analyzed using QIIME package. Summary statistics were calculated for demographic and survey data. Fecal samples were analyzed for 80 females (47 black, 33 white) with a mean age and BMI of 39.9 years and 30.9 kg/m2, respectively. Blacks had a higher average BMI than whites (33.3 vs. 27.5 kg/m2; p=0.003) and larger waist circumference (98.3 vs. 86.6 cm; p<0.01). Measures of alpha diversity indicated similar within-sample gut microbial diversity for black and white women. Beta diversity indicated racial differences using the Bray Curtis (p=0.04) and Unweighted Unifrac (p=0.003) methods, but not Weighted Unifrac (p=0.13). Chronic stress was inversely associated with Bifidobacterium. Adjusted models revealed that black race was associated with a greater abundance of Bacteroides. Further study of the complex relationships between race, behavior, environment and the gut microbiota are warranted.

Gut Microbiome Metagenome and Metatranscriptome in the Context of Colorectal Carcinogenesis Studies

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We report the first population-level investigation of 372 human gut metatranscriptomes and 929 metagenomes from 308 men enrolled in the Health Professionals Follow-up Study who provided detailed short-term and long-term data on diet. From stool collected up to four times/participant over six months, we contrasted microbial taxonomic, metagenomic, and metatranscriptomic functional ecology. We identified a metatranscriptomic "core" of 81 pathways, universally transcribed over time and across participants, often by different microbes. Across time points, within-person taxonomic and functional profile variation was consistently lower than between-person variation over time. Metatranscriptomic profiles were comparably variable within and between subjects, due to higher within-subject longitudinal variation. In exploring the determinants of taxonomic and functional stability, we found prevalence and relative abundance of a taxonomic or metagenomic feature were both correlated with the stability of that feature. Metagenomic instability accounted for ~70% of corresponding metatranscriptomic instability, the rest likely attributable to sources such as regulation. Congruently, among the subset of pathways that were significantly differential among metatranscriptomes, 79% were over- or under-represented consistently across time points. These results provide an initial characterization of gut microbial ecology into core, subject-specific, microbe-specific, and temporally-variable transcription, and they differentiate metagenomically versus metatranscriptomically informative aspects of the human gut microbiome.

A Functional Screen of Crohn's Disease-Associated Microbial Metabolites Identifies Unprecedented Molecules Modifying Mucosal Cell Biology

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Microbial metabolites are an emerging class of modifiers in intestinal mucosal biology. To advance the understanding of direct causal microbial factors contributing to Crohn's disease (CD), we used metagenomic and metabolomic analyses to identify CD-associated microbial metabolites. We evaluated 139 commercial available analytes for their bioactivity using in vitro platforms of epithelial, CD4+ T cell, dendritic and macrophage differentiation and function. We observed a high frequency (~20%) of bioactivity, typically targeting multiple mucosal cell types and functions. Most bioactive metabolites were unprecedented in the literature, and mechanistic analyses uncovered targets in lipid, amino acid, and energy metabolism.

Microbial Modification of Colonic Mucosal Gene Expression Response to a Flaxseed Lignan Extract Intervention in Humans

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Diet is an important risk factor for colorectal cancer (CRC) and dietary constituents are metabolized by gut microbiota. For example, microbial metabolism of plant lignans in high-fiber foods produces bioactive endproducts, such as the enterolignans, enterolactone (ENL) and enterodiol (END). Enterolignan exposure has been associated with lower CRC in recent epidemiologic studies. Lignans have been shown to reduce colon tumorigenesis in animal models, and END and ENL influence cellular pathways important to cancer risk in vitro. Thus, we conducted a 2-period randomized, cross-over intervention in 42 healthy men and women (ages 20-45) to test the effect of a flaxseed lignan supplement (50 mg/d secoisolariciresinol diglucoside) as compared to placebo on: (1) host gene expression in epithelium and stroma from colon biopsies and exfoliated colonocyte RNA extracted from feces; (2) gut microbial community composition, and (3) the interaction of the gut microbiome, enterolignan exposure, and colonic gene expression in high- and low-ENL excreters. Specimens were collected at the end of each of the two 60-d intervention periods. RNA-seq was used to measure differential gene expression in colonic mucosa and fecal exfoliated cells using edgeR and functional analysis with Ingenuity Pathway Analysis (IPA). Fecal homogenate 16S rRNA gene (V1-V3) and metagenomics from in vitro incubations were used to characterize the microbiome along with END and ENL in 24-h urines by GC-MS. In order to elucidate the complex interactions between microbiome, host and diet, master-slave regulatory modeling and LDA classification were used with a mixture of host and microbial features.

A Simple Bacterial Consortium Protects Against the Development of Colon Tumors

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The gut microbiome has emerged as a significant factor in the maintenance of intestinal health and the pathogenesis of disease. The gut microbiota is critical for the development and stimulation of the immune system, facilitating dietary metabolism, and resisting pathogen colonization. On the other hand, pathogenic alterations in the composition of the gut microbiome have been associated with increased susceptibility to intestinal infection, inflammatory bowel disease, and colorectal cancer. We have previously demonstrated that germfree mice have increased susceptibility to epithelial injury-induced colon tumorigenesis compared to conventionally-raised mice. We have subsequently identified a simple defined bacterial community consisting of 11 human gut isolates that can completely suppress the development of tumors in germfree mice. Our data further suggests that the protective effects of this simple community does not require either innate or adaptive immunity, but some activity provided only by live bacteria. Metabolomic and metaportoemic studies are currently ongoing to define bacterial activities associated with tumor suppression.

Modeling the Microbiome in Colorectal Cancer: Emerging Approaches to Hypothesis Testing

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The research and understanding of colorectal cancer (CRC) is being transformed by the findings in the field of the human gut microbiome. Modern sequencing has enabled high-throughput hypothesis generation, rapidly adding new possibilities for cures. And yet, despite the wealth of hypotheses available, having too many paths to follow has also paradoxically slowed progress. The necessity of in silico modeling for hypothesis testing in the microbiome sciences is a product of the diversity of species, functions, and genes—a diversity that outstrips our current experimental capacities. In order to overcome these limitations, we must combine our relatively sparse observations with mechanistically-based predictive modeling coupled with classic approaches to experimental validation.
Here, we present our work on the role of microbially-produced hydrogen sulfide on the etiology of CRC. In our approach, we show how high-throughput sequencing and metabolomics technologies enable in silico modeling of hydrogen sulfide production within the GI tract and how this can be linked with the known genetic categories of CRC. Special focus is given to the multi-scale nature of the modeling approach, which steps from the use of deep metagenomic sequencing for assembling over 80 novel genomes to community metabolic models of the GI microbiome. The latter can then be linked to both metabolomics profiling for validation and dietary interventions for in silico hypothesis testing. Finally, we describe the role of hydrogen sulfide producing microbes in a specific genetic subset of CRC and describe how this work can be used as a template for future discovery and hypothesis testing in other variants of CRC.

Gene-Microbiota Interactions Contribute to the Pathogenesis of Inflammatory Bowel Disease

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Caltech

Inflammatory bowel disease (IBD) is associated with risk variants in the human genome and dysbiosis of the gut microbiome, though unifying principles for these findings remain largely undescribed. The human commensal Bacteroides fragilis delivers immunomodulatory molecules to immune cells via secretion of outer membrane vesicles (OMVs). We reveal that OMVs require IBD-associated genes, ATG16L1 and NOD2, to activate a non-canonical autophagy pathway during protection from colitis. ATG16L1-deficient dendritic cells do not induce regulatory T cells (Treg) to suppress mucosal inflammation. Immune cells from human subjects with a major risk variant in ATG16L1 are defective in Treg responses to OMVs. We propose that polymorphisms in susceptibility genes promote disease through defects in 'sensing' protective signals from the microbiome, defining a potentially critical gene-environment etiology for IBD.

Early Life Stress/Pain Experience Imprints Gut Microbiome in Preterm Infants

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Purpose: The study purpose was to investigate linkages between early life stress including accumulated painful experience and infant neurobehavioral outcomes modulated by the brain-gut-microbiota axis. We hypothesized that that premature infants subjected to stressful early life experiences develop an altered gut microbiome increasing risk for neurodevelopmental morbidity. **Methods:** Fifty preterm infants were recruited at birth and followed-up for 3-4 weeks during neonatal intensive care hospitalization. Outcome measurements were gut microbiota (16S rRNA sequencing), early life stress, and neurodevelopmental outcomes. Stool samples and stress levels were measured daily and neurodevelopmental outcomes were examined at 35-36 weeks post-menstrual age. Exploratory data analysis was conducted with a focus on the evolution in each variable's distribution over time and linkages among variables. Predictions for neurodevelopmental outcomes were also analyzed using multiple regressions models. **Results:** Preterm infants experienced large amount of painful/stressful event in their early life during the NICU stay. Acute and chronic pain/stressors and contacts were significant predictors for neurodevelopmental responses. Preterm infants' gut microbiome patterns were diverse among individual infants. Pain/stressor scores accounted for greater than 10% of the variability seen in the microbiome community and there was an association between the gut microbiome diversity and neurodevelopmental outcomes. Understanding mechanisms by which early life experience alters neurodevelopment via the brain-gut-microbiota axis will help clinicians to develop neuroprotective strategies to better predict outcomes and to provide interventions.

Dynamics of the Oral, Vaginal, and Gut Microbiome of African American Women With Full-Term Pregnancies

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Purpose: African American (AA) women have increased risk for preterm birth (PTB). The oral, vaginal, and gut microbiome are posited to influence risk, but existing research has not adequately characterized the structure and dynamics of the microbiome of AA women whose pregnancies end in full term vs. preterm birth – a first step in understanding how variation in the microbiome may contribute to inter-race disparities. **Methods:** Our 5-year study, Biobehavioral Determinants of the Microbiome and Preterm Birth in Black Women, enrolls pregnant AA women at 8-14 weeks. Participants complete questionnaires and provide oral, vaginal, and gut microbiome samples at enrollment and 24-30 weeks. Chart review identifies pregnancy outcomes. For the first 184 women completing the study, DNA was extracted and sequencing of the V3 and V4 regions of the 16S rRNA gene was conducted. Processing and mapping were completed with QIIME and OTUs mapped to Greengenes version 13_8. Data were rarified to 14,900 reads. Community state types (CSTs) and diversity measures at each site and time were identified. **Results:** Microbiome analyses are described for the first 32 women delivering full term infants; remaining analyses are underway. Shannon Diversity was highest in oral and gut microbiome, with little change over pregnancy. Only 22% of women whose pregnancy resulted in full-term birth had vaginal microbiome at the first prenatal visit dominated by protective lactobacilli. **Conclusions:** By studying within race variation in the microbiome throughout pregnancy, progress is made in discerning the role of the microbiome in contributing to inter-race disparities in birth outcomes.

The Gut-Microbiome-Brain Axis in Neurodevelopmental Disorders

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The concept that commensal bacteria in the gut could have a profound influence on brain function was unthinkable just a few years ago. The idea that a single bacterial species could be used as a treatment for developmental disorders is unthinkable today. One of the first links between the microbiome and brain processes was reported in the field of autism spectrum disorder (ASD), where patients with ASD co-present behavioral abnormalities and gastrointestinal symptoms. This led to the speculation that changes in gut microbiome could increase the risk of neuropsychiatric disorders such as ASD. However, how changes in bacteria that inhabit in our intestine could influence brain development and function remains unknown. Our findings link these two axes of dysfunction. We found that maternal high fat diet (MHFD), which is known to elevate the risk of ASD, induces a shift in microbial ecology that has a direct negative impact on offspring's social behavior. These social deficits and changes in gut microbiome are prevented by co-housing MHFD offspring with mice born of mothers receiving regular diet and transferable to germ-free mice upon fecal-transplantation. Notably, we also found that MHFD-induced changes in the microbiome block long-lasting neural adaptation in the dopamine reward system. More importantly, using metagenomics and selective microbiota reconstitution, we identified a bacterial strain that restores both synaptic function and social behaviors by correcting the levels of oxytocin, the "social" hormone, in the brain. Our results causally link maternal diet, gut microbiota dysbiosis, changes in synaptic plasticity and abnormal social behavior and identify a potential probiotic therapy for ASD-like symptoms.

HMP DACC Data Portal

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The HMP DACC Data Portal (http://portal.hmpdacc.org) provides a unified view of microbiome data produced by the NIH Human Microbiome Project (HMP) and subsequent NIH Integrative Human Microbiome Project (HMP2). These data comprise a variety of data types (e.g., 16S, whole metagenomic shotgun, host and microbial transcriptome, lipidome, metabolome, proteome, and cytokine), file formats, and rich subject metadata coming from multiple studies, several of which feature both large cohorts and longitudinal data. The HMP DACC Data Portal is based on the NCI's open source GDC Portal UI (https://github.com/NCI-GDC/portal-ui), but modified to serve metagenomic rather than cancer data and to interoperate with the DACC's Open Science Data Framework (OSDF) data storage backend. Users can rapidly identify datasets of interest with either the facet search facility or an advanced query interface and selected datasets may be added to a shopping cart. From there a manifest file can be downloaded and passed to a standalone client program to download bulk data en masse. The standalone client is capable of resuming batch downloads and can optionally take advantage of the Amazon/S3-hosted HMP data when running in the cloud on Amazon EC2.

Human Microbiome Project Data Resources

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As the Data Coordination Center (DCC) for the Integrative Human Microbiome Project (iHMP), we provide a central repository for querying and accessing all HMP and iHMP data. To this end, we have worked closely with data managers from each of the four iHMP institutions to develop a comprehensive data storage schema based upon the Open Science Data Framework (OSDF). This serves as the backbone for our HMP Data Portal, which allows intuitive and interactive searching as well as the ability to build custom cohorts/data sets for download or direct incorporation into analysis tools such as MetaViz. Schemas and associated API and submission tools are publicly available at https://github.com/ihmpdcc. The HMP data portal, as well as project details, SOPs and tools, is available at the comprehensive HMP/iHMP DCC website, www.hmpdacc.org.

Butyrate Protects Gut-Liver Axis During Chronic-Binge Ethanol Exposure

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Ethanol-induced gut dysbiosis is associated with altered gut permeability and endotoxemia. Gut dysbiosis is associated with alterations in metabolic byproducts, inflammation and immune suppression. Butyrate, a fermentation byproduct of the gut microbiota, is essential for gut health. Chronic ethanol exposure is associated with depleted butyrate levels. This study investigated whether prophylactic butyrate could mitigate intestinal and liver injury induced by chronic-binge ethanol feeding.

Methods: Ethanol feeding with chronic-binge (10 d, 5% vol/vol)-binge (5 g/kg) exposure was conducted to gain understanding of tributyrin's effect in a mouse model more clinically reflective of early stages of alcoholic hepatitis. Glycerol (control) or tributyrin was provided via a liquid diet (5mM) and oral gavage (2.5 mM). Intestine, plasma and liver were analyzed for markers of injury and inflammation. Caco-2 monolayers exposed to ethanol (40 mM) ± sodium butyrate (5 mM) tested butyrate's direct effects on intestinal epithelial cells. **Results:** Ethanol induced hepatic mRNA expression of toll-like receptors, protein expression of TNFα and losses in intestinal barrier function in vitro and in vivo; however, butyrate co-treatment reduced this response. Ethanol feeding also blunted intestinal immune responses which were maintained with tributyrin co-treatment. Variances in hepatic localization of leukocytes and apoptotic hepatocytes between ethanol-fed treatment groups were identified. **Summary:** Prophylactic tributyrin can mitigate intestinal barrier disruption, intestinal immune suppression and liver injury induced by chronic-binge ethanol exposure and may provide a novel strategy to prevent early-stage alcohol hepatitis.

Commensal Composition and Efficacy of Microbiota-Based Treatments Are Influenced by Innate Immunity

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The effect of chronic inflammation on the composition of the colonic microbiota is not well understood, making the development of microbiota-associated therapies difficult. Using a model of inflammation-associated colorectal cancer (CRC) we show that restoration of specific probiotic commensals lost during tumorigenesis profoundly reduced tumor burden by preventing changes in Proteobacteria and suppressing inflammation through a TLR6-dependent induction of IL-10. Attenuated TLR6 signaling was associated with worse cancer outcomes in a subset of CRC patients and an increase in proximal tumors in our mouse model. Analysis of the proximal colon from TLR6-deficient mice revealed significant differences in the composition of the microbiota. This tissue was also unresponsive to treatment with recombinant IL-10 or by restoring probiotic commensals. Altogether, these results suggest that while microbiota-associated biotherapies are more effective if tailored to an individual, genetic and immunologic factors must be taken into account as they can influence the treatment efficacy.

Exploring Bacteriophage Community Composition During Intestinal Colitis

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The dysregulation of intestinal bacterial communities can lead to inflammatory bowel diseases (IBD). In addition to bacteria, the intestine harbors eukaryotic and prokaryotic viruses and viruses that infect bacteria called bacteriophages (phages), dominate. Phage numbers are elevated at the intestinal mucosal surface and specific phage species increase in abundance in IBD patients. This suggests that phages play an unidentified role in IBD and may be relevant biomarkers for the disease. We have developed a method to identify phages within metagenomes of the intestinal microbiota. Our method relies on the quantitative comparison of contig abundances between metagenomes from the complete microbiota and virus enrichments of that same microbiota. We have applied this method to study phage communities in a mouse model of immune cell induced intestinal colitis. We discovered that colitis alters the intestinal phage population at the height of disease. Using phage contig annotation and analysis of clustered regularly interspaced short palindromic repeat (CRISPR) spacer sequences to match phage contigs to bacterial hosts, we observed a decrease in phages associated with beneficial commensal bacteria, whereas the phages of overt intestinal pathogenic bacteria became more abundant during colitis. These results are consistent with phage communities recovered from human IBD patients. Our data suggest that the immune system imposes pressure on the microbiota altering phage community composition. A deeper understanding of how the immune system shapes phage communities during intestinal health and disease will illuminate strategies for the use of phages as therapeutic tools to manipulate the microbiota and improve human health.

Distinct Microbiota in the Cervicovaginal Space Are Associated With Spontaneous Preterm Birth

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Objective: Changes in microbial communities have been implicated in both health and disease. Investigations into the association between the cervicovaginal (CV) microbiota and spontaneous preterm birth (sPTB) have been limited in scope and sample size. **Study Design:** A prospective cohort of singleton pregnancies were enrolled (n=2000). Biospecimens were collected at 3 time points in pregnancy (16-20, 20-24, 24-28 weeks). All cases of PTB were adjudicated by the PI. From the larger cohort, a nested case-control was performed with 80 SPTB cases and 320 term controls that were frequency matched by race to the cases. 16S rRNA gene analyses were performed to characterize the composition and structure of the CV microbiota. Phylotype analyses were performed for the relative and absolute abundance in association with sPTB. **Results:** 127 phylotypes were detected in all samples. Significant associations were demonstrated between specific bacteria, in both a positive and negative manner, with sPTB. Racial differences in these associations were evident. Bifidobacterium species were noted to be significantly protective against SPTB at all gestational time points while BVAB2, BVAB3 and Mobiluncus were associated with a dramatic increase risk of SPTB (all q-values <0.0001). **Conclusion:** CV microbiota are significantly associated with SPTB. Targeting the bacteria that are associated with an increased risk of SPTB and/or enhancing the presence of the protective bacteria may serve as new

therapies to reduce the rate of PTB. With this new evidence, these types of studies should become a research priority. (R01NR014784)

Open Science Data Framework

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The Open Science Data Framework (OSDF) provides a software framework and RESTful API for storing and retrieving project metadata and conducting bioinformatics analyses across several research organizations in a standard way. OSDF supports a diverse set of users, including (1) sequence generators store and process raw data (2) tool and pipeline developers that need access to reference data sets, and (3) web-based resources that need real-time querying of reference data. Genomics communities and projects such as the HMP (Human Microbiome Project) and the iHMP (Integrative Human Microbiome Project) have used OSDF to store and track transcriptomic data, metagenomic data. OSDF also enables users to conduct analyses that include human variation detection, transcriptome analysis, epigenetic analysis, and microbiome analysis.

Predictors of Preterm Birth in a Longitudinal, Multi-Omic Study of the Vaginal Microbiome

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Preterm births occurring at less than 37 weeks gestation account for approximately 1 in 10 births in the United States. The incidence has not decreased despite significant efforts. It is clear that the etiologies of preterm birth are multifactorial; however, the processes leading to complications in pregnancy are still poorly defined. Ascension of microorganisms from the vagina is the most common pathway for intrauterine infection, which can cause preterm premature rupture of membranes (PPROM), fetal compromise, preterm labor and other complications. As part of the integrative Human Microbiome Project (iHMP), we performed a longitudinal, multi-omic study of ~1,500 women through the Multi-Omic Microbiome Study-Pregnancy Initiative (MOMS-PI). Technologies include whole metagenome shotgun sequencing, whole metatranscriptomic sequence analysis, cytokine profiling and 16S rRNA gene surveys. We analyzed vaginal, multi-omic data from a subset of 47 singleton pregnancies that resulted in preterm delivery and matched term controls. We also assayed the vaginal microbiome composition of an additional ~100 preterm births and controls from the Vaginal Human Microbiome Project (VaHMP) and the Global Alliance to Prevent Prematurity and Stillbirth MOMS-PI cohorts. Our analyses led to the identification of candidate signatures for adverse pregnancy outcomes, which provide insights into the pathways implicated in pregnancy complications.

Associations Between Vaginal Microbiota and Genitourinary Symptoms of Menopause

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Objective: We conducted both cross-sectional and longitudinal evaluation of associations between the composition of the vaginal microbiota and genitourinary symptoms, serum estrogen, and vaginal glycogen in post-menopausal women enrolled in a trial of treatment for hot flashes. **Methods:** A total of 88 women ages 40-62 enrolled in a randomized trial of oral estradiol or oral venlafaxine vs. placebo for hot flashes consented to provide vaginal swabs and a blood sample at enrollment. Of those, 30 (34%) both reported vulvovaginal symptoms at enrollment and provided longitudinal samples at 4 and 8 weeks. Bacterial communities were characterized using 16S rRNA PCR and deep sequencing targeting the V3-V4 region. Quantities of *Lactobacillus crispatus* and *L. iners* were measured using qPCR. Self-reported genitourinary symptoms included: 1) presence and severity of individual symptoms and 2) identification of most bothersome symptom. Glycogen was measured fluorometrically from swab eluate. Serum estradiol (E2) and estrone (E1) were measured by liquid chromatography/mass spectrometry. Associations between bacteria, symptoms, glycogen, and serum estrogens were tested by linear regression or Wilcoxon signed-rank test, adjusted for multiple comparisons. Comparisons between groups used Kruskall-Wallis or Fisher's exact test, and between timepoints using signrank or McNemars tests. **Results:** At baseline, 33 (38%) women had a vaginal microbiota dominated by *Lactobacillus* species, 25 (28%) had *Lactobacillus* present as a minority population and 30 (34%) had no *Lactobacillus* species detected by 16S rRNA sequencing. Over half (53%) reported ≥ 1 vulvovaginal symptom (most commonly dryness), but symptoms were not associated with the presence of *Lactobacillus* species. Women with *Lactobacillus* dominant communities had higher unconjugated serum estrone, but no difference in vaginal glycogen levels, compared to those with non-*Lactobacillus* dominant communities. Higher serum E2 and E1 were not significantly associated with higher vaginal glycogen, nor detection of individual genera. Of the 30 women included in the longitudinal analysis, 21 (70%) had improvement in their most bothersome symptom (MBS) over the course of the study, and 9 (30%) had no improvement or worsening of the MBS. There was no significant variation in *Lactobacillus* dominance, detection of or quantity of *L. crispatus* or *L. iners* at enrollment or 8-week follow-up between women who did and did not have improvement in MBS. A higher level of bacterial community diversity was observed in women whose symptoms did not improve relative to those with improvement, but this difference did not reach statistical significance. Vaginal glycogen, serum estradiol (unconjugated and total) and unconjugated estriol all increased significantly in women whose MBS improved compared to women without improvement. Greater MBS improvement was seen in women receiving active treatment (82%) [estradiol (7/8) or venlafaxine (7/9)] vs. placebo (7/13; 54%), but this difference was not statistically significant, likely due to small sample size. *Lactobacillus* detection and dominance showed little association with receipt of active treatment. **Conclusions**: Presence of *Lactobacillus*-dominant vaginal microbiota was not significantly associated with fewer vulvovaginal symptoms. In women with vulvovaginal symptoms, *Lactobacillus*-dominance of vaginal microbiota was not significantly associated with improvement in genitourinary symptoms of menopause, regardless of treatment assignment.

Characterizing the Role of Vaginal Veillonellaceae Species in Women's Reproductive Health and Pregnancy

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Two vaginal phylotypes provisionally assigned to the genus Megasphaera have been repeatedly associated with bacterial vaginosis (BV) and negative reproductive health outcomes including preterm premature rupture of membranes (PPROM) and spontaneous preterm labor. We cultivated three vaginal 'Megasphaera' clones and in combination with publicly deposited genomes, performed a comparative genomic and phylogenetic analysis of three 'Megasphaera' phylotype 1 and three 'Megasphaera' phylotype 2 genomes. Using bioinformatics and biological measures, we determined that the phylotypes represent two distinct species with differential genomic structure, predicted functional potential, and clinical associations that may be best classified as a novel vaginal-specific genus belonging to the family Veillonellaceae. Herein, we propose the designation Veillonellaceae phylotype 1 (VLN1) and Veillonellaceae phylotype 2 (VLN2). Both phylotypes were associated with vaginal symptoms and diagnosis of BV, while VLN1 exhibited a stronger association with the condition. We also observed intriguing associations with pregnancy in a cohort of 842 case matched pregnant and non-pregnant women. Given the repeated association of VLN1 with negative pregnancy outcomes and a single paper reporting that this organism is capable of invading the upper genital tract, VLN1 is of great interest in elucidating bacterial contributions to negative pregnancy outcomes. To validate our findings, we analyzed the prevalence of both phylotypes in the MOMS-PI cohort, a group of over 1,000 women sampled throughout pregnancy, to assess the prevalence of the two organisms, their dynamics throughout pregnancy and associations with clinical data and pregnancy outcome.

Changes in the Gut Microbiota by Prenylated Flavonoid Supplementation Are Associated With Improvements in Dysfunctional Glucose and Lipid Metabolism in Mice Fed a High-Fat Diet

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The prenylated flavonoid xanthohumol (XN) found in hops and beer improves dysfunctional glucose and lipid metabolism in preclinical animal models of diet-induced obesity (DIO) and metabolic syndrome (MetS). XN binds to the farnesoid X receptor (FXR) and regulates host genes involved in metabolism of cholesterol into bile acids. XN also induces cathelicidin antimicrobial peptide (CAMP) gene expression via the FXR. We hypothesize that consumption of XN by mice feed a high-fat diet induces CAMP and shapes the composition of the gut microbiota. Furthermore, the gut microbiota metabolizes XN into 8-prenylnaringenenin and □, □-dihydro-XN (DXN) that may function as FXR ligands. This diet-microbe-host interaction may explain, in part, how XN in ameliorates obesity and MetS. We compared DXN and a related XN metabolite tetrahydro-XN (TXN) with XN by feeding C57BL/6J mice a high-fat diet containing these compounds for 14 weeks. Mice administered XN, DXN or TXN showed similar improvements of impaired glucose tolerance compared to the control; however, the derivatives decreased plasma insulin and leptin better than XN. We sequenced the 16 rRNA genes of the microbes present in the feces of

each animal. We observed statistically significant shifts in the structure and membership of the microbiota. The compounds significantly decreased the percentages of Bacteroidetes and Tenernicutes. In contrast, they significantly increased Firmicutes, Proteobacteria (DXN and TXN), and Verrucomicrobia (DXN and TXN). We are currently identifying specific genera that correlate with weight gain, fasting glucose and levels of leptin, cholesterol and insulin. Our data support a role for the microbiota in conferring the benefits of XN consumption on DIO.

The Preterm Infant Microbiome: Growth, Health, and Development at 2 and 4 Years of Age

Maureen Groer, Larry Dishaw, Kathleen Armstrong, Elizabeth Miller, Jack Gilbert, Alyson Yee

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Preterm infants have abnormal microbial colonization in early life. They are often delivered via Caesarean section, and have high rates of formula feeding, invasive procedures, antibiotics, and medications that alter gastrointestinal pH, which all contribute to the assembly of the microbiome. We hypothesized that microbial community structure would be predicted by many of these factors. We enrolled 78 preterm infants and characterized the stool microbiome from admission through 6 weeks of age. We analyzed the samples by 16S rRNA amplicon sequencing. We found that the preterm infants' gut microbiome developed a striking dominance of Proteobacteria and increased diversity over time. The distribution of bacterial taxa was predictive of the incidence of necrotizing enterocolitis and the use of antibiotics.

We then demonstrated that these infants had significantly greater bacterial diversity and less interindividual variability as toddlers, suggesting the microbiome normalized despite the abnormal founding microbiome. Oligotype analysis suggested that strains of Enterobacteriaceae and Bifidobacterium that colonized the infants during their NICU stay were still associated with stool at age 3. Twenty one toddlers are being followed through early childhood until 5 years of age with measures of stool microbiome, maternal microbiome, growth, health and development. About half of these children have some developmental delay or behavioral issues. They display an obesogenic phenotype We are currently analyzing these characteristics in relationship to both the NICU microbiome and the childhood and maternal microbiome.

Omega-3 Fatty Acids Protect Murine Fetuses From Bacteria-Induced Placental Inflammation Originating From Maternal Endothelial Cells

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Intrauterine infection is a leading cause of adverse pregnancy outcomes (APOs) such as preterm delivery, stillbirth, and neonatal sepsis . Omega-3 fatty acids and their metabolites have been found to be beneficial in a wide spectrum of infectious diseases including periodontal disease, respiratory tract infections and sepsis . We have previously shown that Fusobacterium nucleatum, a Gram-negative oral commensal bacterium frequently detected in intrauterine infection, colonizes the murine placenta through hematogenous transmission and causes intrauterine inflammation and fetal demise . However, the detailed mechanisms of pathogenesis were not known. Using mouse genetics, we now demonstrate

that F. nucleatum triggers placental inflammation through TLR4-medaited signaling in maternal endothelial cells. We further demonstrate that omega-3 fatty acids suppress bacteria-induced inflammatory responses in endothelial cells, and protect murine fetuses against infection. Our study reveals a novel mechanism by which microbial infections affect pregnancy and establishes a potential use of omega-3 fatty acids to protect against intrauterine infection and APO.

Early Life Colonization of the Nasopharyngeal Microbiome: A Longitudinal Study in The Gambia

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Streptococcus pneumoniae is the most common cause of pneumonia in children under 5 worldwide, resulting in an estimated 1 million deaths each year with the majority in developing countries. To mitigate the morbidity and mortality of this disease, pneumococcal conjugate vaccine (PCV) is administered. Most validation and investigative studies of these PCVs were performed in developed countries, and now national vaccine programs are being implemented throughout the world. In The Gambia, such a national program began several years ago with the implementation of the 7-valent PCV, moving to the 13-valent PCV to cover additional serotypes relevant within The Gambia. This study enrolled infants within The Gambia to 1) assess the patterns of pneumococcal carriage in the first two years of life with widespread use of PCV13, 2) characterize the normal development of the nasopharyngeal microbiome in the first two years of life, and 3) study the greater environmental context for the child, including the microbes on the mother and household contacts, to reveal routes of colonization.

We conducted a longitudinal study, enrolling 120 newborns in The Gambia between March and September 2013 and followed them for the first two years of life. Risk factor data and nasopharyngeal samples (NPS) were collected each month in the first year and every three months in the second year, including the three visits when the infants received the PCV13.

With this rich dataset, we have described the characteristics of the nasopharyngeal microbiome among our cohort, as well as the variability of the microbiome during the first two years of life. Dirichlet Multinomial mixture models are being used to assess demographic and risk factors for colonization.

Development of New Genetic Tools to Determine the Role of Siderophores in Clostridium Difficile Pathogenesis

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Clostridium difficile (Cd) is the leading cause of hospital acquired infectious diarrhea. Antibiotic treatment leads to reduced microbial diversity in the gut, allowing colonization by Cd. Iron is an essential nutrient used by host cells and most bacterial species. As a result of numerous mammalian storage proteins, very little free iron is present in a mammalian host. Bacteria have evolved numerous mechanisms for acquiring this iron, including small molecules with a very high affinity for iron called siderophores. The genomes of many Cd strains encode genes with annotated roles in siderophores

import, but lack known siderophore biosynthetic genes. Analysis of sequenced Cd genomes identified genes for biosynthesis of the siderophore yersiniabactin (Yb) in a subset of strains. We identified orthologs of the genes for Yb biosynthesis in 28/166 tested strains. We hypothesize that Yb plays a role in Cd pathogenesis and may contribute to increased disease severity observed for some isolates. To test this hypothesis, we will make isogenic mutants lacking the Yb biosynthesis pathway and examine its role in pathogenesis. Making mutants in clinical isolates of Cd has proven difficult. Current methods, including ClosTron and codA based allelic exchange, allow for genetic manipulation of one or two strains, but are not broadly applicable to all clinical isolates and have not worked to date in strains harboring the genes for Yb biosynthesis. We are currently developing a method to create clean deletions in these strains, including the highly virulent laboratory strain VPI 10463, which encodes for Yb biosynthesis. Development of this method will be crucial to examine differences between Cd clinical isolates, including the role of Yb. We predict such differences will provide insight into the pathogenesis of Cd strains leading to improved treatment options.

Functional Dynamics of the Gut Microbiome in Healthy Subjects During and After 6 Months of Consumption of Probiotic Lactobacillus Rhamnosus GG ATCC 53103 vs. Placebo

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Probiotics are believed to have health benefits but little is known about the mechanisms by which these purported effects occur. We conducted a phase I, double-blinded, placebo controlled randomized trial under an Investigational New Drug (IND) application to evaluate the safety of a single-organism probiotic, Lactobacillus rhamnosus GG ATCC 53103 (LGG), and its effects the structure and functional dynamics of the gut microbiota. The study was conducted in 50 healthy adults aged 18-50, 39 of whom received LGG (2×1010 colony forming units daily) for 6 months and 11 received matching placebo. All were followed for an additional 6 months off study drug. Stool samples were obtained prior to the start of study drug, at month 1, 3 and 6 while taking study drug and at month 7 and 12 after completing study drug. There were no serious adverse events. The mechanistic studies were conducted in the most compliant subjects (based on pill counts and LGG culture) – 6 receiving LGG and 6 receiving placebo. The relative abundance of Lactobacillus rhamnosus transcripts was significantly greater after consuming LGG for 28 days and 3 months, compared to baseline levels in LGG the group. LGG was also associated with an increase in the expression of fatty acid biosynthesis genes that contribute to butyrate biosynthesis. In LGG group, there was an increase in the expression of PTS genes in Roseburia and a decrease in the expression of chemotaxis genes.

Modulation of Neointimal Hyperplasia Severity in Rats by Commensal Microbial Transfer

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Background: Neointimal hyperplasia is a major contributor to restenosis after arterial interventions. The genetic and environmental mechanisms underlying the variable propensity for neointimal hyperplasia between individuals are not well understood. One possible modulator could be commensal gut

microbes. **Methods:** We cohoused genetically different rats (Lewis [LE] and Sprague Dawley [SD]) which harbor different commensal microbes and compared neointimal hyperplasia after carotid angioplasty in the cohoused and non-cohoused cohorts. 16S sequencing was used to monitor fecal samples. **Results:** We observed that differences in neointimal hyperplasia between non-cohoused LE and SD rats (median intima+media [I+M] area 0.12 mm2 LE vs. 0.26 mm2 SD, P<.0001) were mitigated when rats are cohoused, suggesting an environmental effect that outweighs the genetic influence. Specifically, I+M area decreased by 23% in SD rats that were cohoused with LE rats (P<.0001), and there was a trend towards a 10% increase in I+M area in cohoused LE rats. Principal component analysis revealed that fecal samples from cohoused rats diverged from non-cohoused rats in both strains (P<.001 SD, P=.008 LE). The greatest change was cohoused SD samples becoming similar to non-cohoused LE samples over time, which correlates with the carotid morphometric data. Comparative analysis showed that abundance of the bacterial genera Peptococcus and Blautia negatively correlated with I+M area in both strains (P<.001; Spearman's ρ -0.8). Ongoing studies will delineate the potential causative relationship between these microbes and neointimal hyperplasia. **Conclusions:** Gut microbes potentially regulate the severity of arterial remodeling after vascular interventions.

Metabolomic Profiling of the Infant Stool Microbiota: Associations With Delivery Mode and Diet in the New Hampshire Birth Cohort Study Metabolomic Profiling of the Infant Stool Microbiota

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The intestinal microbiota plays a critical role in infant development, with important functions for nutrient metabolism and immune maturation. Using 1H NMR metabolomic profiling, we characterized 100 stool samples collected from six week old infants enrolled in the New Hampshire Birth Cohort Study to identify functional relationships between the stool microbiota and delivery mode and feeding method. We abstracted delivery mode from the delivery medical record and ascertained feeding practices with a telephone survey. We used multivariate analysis methods to reduce the dimensionality of metabolomics profiles and enable their visualization by study groups defined by delivery mode (vaginal vs. Cesarean) and feeding during the first six weeks (exclusively breast fed vs. exclusively formula fed/combination fed). Statistical tests were conducted using a two-sided t-test with correction for unequal variances. Library-matched metabolites that were important to differentiating the study groups were analyzed for metabolite set enrichment analysis using MetaboAnalyst. Our analyses indicated discrimination by both delivery mode and diet. We identified 37 metabolites that were important for differentiating delivery mode groups and 54 metabolites that were important for differentiating feeding groups, including 29 that differentiated both. We conclude that the microbial communities colonizing the gastrointestinal tracts of infants are functionally distinct when compared according to delivery mode and feeding groups. Furthermore, different but overlapping sets of metabolites and metabolic pathways define delivery mode and diet metabotypes.

Fecal Bile Acids and Steroids Correlate With Abdominal Pain in Children With Irritable Bowel Syndrome

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Purpose: Childhood irritable bowel syndrome (IBS) affects up to 20% of children worldwide. Altered gut microbial and biochemical composition are reported to correlate with symptoms of IBS. Our study explored the role of microbial-metabolite interactions by determining whether the fecal metabolome: (1) differed between healthy control (HC) and IBS children; (2) correlated with abdominal pain and/or microbial community composition and biochemical capacity. **Methods:** Children (7-12 years) with IBS (n=36; Rome III criteria) and HC (n=34) were enrolled. All completed questionnaires and a 2-week diary which captured pain frequency/severity and stooling frequency/form. A fecal specimen collected during diary completion was processed for 16S rRNA and shotgun metagenomic sequencing, unbiased global metabolomics and quantitative MS. Group differences were assessed by Mann-Whitney-Wilcoxon testing, correcting for false discovery rates. Multi-omic analysis was performed (Spearman rank sum correlations). **Results:** Fecal microbiome and metabolite composition were similar in HC and IBS. Significant correlations were recorded between abdominal pain and secondary bile acids ($r>0.34$; $p<0.02$) and steroids ($r>0.31$; $p<0.04$). These pathways correlated significantly with abdominal pain and relative abundances of genera Oscilibacter, Eggerthella, Haemophilus, Ruminococcus, and Lactobacillus. Abdominal pain correlated significantly with the genus Alistipes. **Conclusion:** We identified a previously unappreciated relationship between a common cholesterol-based biochemical pathway and abdominal pain in a well-characterized pediatric IBS cohort. We link this new disease-associated biochemical pathway with shifts in microbial community composition.

Metabolic Modeling of the Vaginal Microbiome: Methods and Progress Updates

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The composition and collective function of the human vaginal microbiome has potential health implications including bacterial vaginosis and preterm birth during pregnancy. The vaginal microbiome is a community of numerous microorganisms and changes in composition over short time periods that can include several major shifts in composition during pregnancy. To study the interplay of discrete microbes within the microbiome and how they affect the composition of the consortium and female health, a computational pipeline has been developed to model the vaginal microbiome using metagenomics data and includes the ability to integrate disparate experimental data (e.g., metatranscriptomic data). This poster will provide information on the components of the computational pipeline and provide an update on progress on implementing the pipeline to construct and analyze clinical vaginal microbiome data.

Host-Bacteria Genome Interactions in Tumors

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Bacteria and animals are known to share DNA through horizontal or lateral gene transfer as seen with LINE element integrations in N. gonorrheae and ubiquitous Wolbachia integrations in their diverse arthropod and nematode hosts. Through a secondary analysis of public cancer genome sequencing data, we have measured the extent to which bacterial DNA integrations (BDIs) occur into the somatic human genome, and concomitantly measured the microbial diversity within cancer samples. Specific tumor samples are enriched for BDIs and have a corresponding enrichment of that microbe in the genome sequencing data. Modeling of the integrations suggests they occur in the 5'-UTR of transcripts that have been associated with oncogenesis and that they may form secondary structures that have the potential to alter the transcript structure. Laboratory-based reconstructions of those integrations suggest that they lead to dysregulation of the gene in a strand-specific manner, meaning inversions of the integrations do not alter transcription. Several bacterial enrichments in the sequencing data had associations that led to them being deemed contamination, usually at the sequencing center or the tissue source site, but the ones associated with BDIs did not have those attributes, although contamination cannot be ruled out. BDIs that meet our criteria were not identified in the samples with contamination. To understand the provenance of reads supporting BDIs better, we have sequenced bacteria-infected human cells to measure the rate of chimera artifact formation that would mimic BDIs. These results will be highlighted and the context for these results will be discussed.

Analysis of the Vaginal Microbiome in Health and Disease

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Virginia Commonwealth University

Dysbiosis of the vaginal microbiome has been implicated in several pregnancy complications and adverse health outcomes. Vaginal complaints are one of the most common reasons for women seeking medical attention worldwide and clinical symptoms are often misdiagnosed. As part of the Vaginal Human Microbiome Project at Virginia Commonwealth University (VaHMP), we sampled close to 5,000 women from the clinical setting to explore the relationship of the vaginal microbiome with various physiological and infectious conditions. In this unparalleled study characterizing the vaginal microbiome, we analyzed samples using 16S rRNA taxonomic profiles and performed deep whole metagenomics sequencing on a subset of women with symptomatic BV. Species-level analysis of vaginal microbiome profiles reveals how the samples further clustered into distinct 'vagitypes', driven by the predominant bacterial species in the sample. These vagitypes include several Lactobacillus types (L. crispatus, L. iners, L. gasseri, L. jensenii), a Gardnerella vaginalis type, a type dominated by bacterial vaginosis-associated bacterium (BVAB1), and many more rare vagitypes dominated by minor vaginal taxa. A complete species-level analysis also reveals that vagitypes are correlated with clinical features such as vaginal pH, clinical diagnosis of bacterial vaginosis, pregnancy outcomes, age, diabetes status, STI status, diet, sexual history and contraceptive use. Overall, this study reveals insights into the diversity of the vaginal microbiome and has important implications for future studies exploring how urogenital health is defined particularly among women of diverse ethnicities.

Synergy Between Genes and the Environment: The Effect of the Microbiome and Host Genetic Variation on Exposures to Enterolignans and Steroid Hormones in Post-Menopausal European American and African American Women

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Lignans are phytoestrogens implicated as dietary factors in breast cancer etiology due to structural and functional similarities to endogenous estrogens. Breast cancer risk has been positively associated with serum and urinary steroid hormones, and may be modified by race. Importantly, steroid hormone metabolism and excretion can be modified by diet. Central to this is the conversion of dietary lignans by the gut microbiome to enterolignans: enterodiol (END) and enterolactone (ENL). Our study objectives are (1) to determine how variation in gut microbial community composition, and steroid hormone and xenobiotic metabolizing genes affects the metabolism of lignans and steroid hormones, and (2) how these associations differ for African American and European American women. We conducted a randomized cross-over design 6-week intervention in healthy, postmenopausal women (79 African American and 113 European American) to test the effect of 10g/d of ground flaxseed on (1) production of END and ENL, (2) circulating sex steroid hormones, and (3) the gut microbiome. Specimens were collected at baseline and the end of each intervention period. We measured the microbiome by sequencing (MiSeq) the V1-V3 region of the 16S rRNA gene and imputed functional genes, SNP analysis by Sequenom MassArray for variation in steroid hormone metabolism, and GC/MS to measure 24 hour urinary END and ENL. Direct and indirect effects of study variables on these measures will be modeled by traceable regressions to gain insight into functional mechanisms that may influence racial disparities in breast cancer outcomes. Supported by U01 CA161809.

Commensal Mucin Degradation Stimulates Respiratory Pathogen Growth in Chronic Lower Airway Disease

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The CF lung microbiota plays a critical role in the progression of airway disease. While interactions between canonical pathogens (e.g., Pseudomonas aeruginosa and Staphyloccocus aureus) have been described in detail, the role of commensal bacteria (notably, oral-associated anaerobes) in disease progression is unknown. To address these interactions, we used purified airway mucins as a sole carbon source to assess the ability of P. aeruginosa to directly utilize respiratory secretions as nutrients in the presence and absence of mucin-degrading anaerobes. P. aeruginosa was unable to grow unless co-cultured in the presence of an oral-derived anaerobic consortium. 16S rRNA gene sequencing demonstrated that four genera – Fusobacterium, Veillonella, Prevotella, Streptococcus – were key mucin degraders that facilitated Pseudomonas growth. Targeted metabolomics and mutant analyses identified propionate and acetate as the central mucin-derived metabolites involved in this cross-feeding relationship. RNAseq was then used to demonstrate that P. aeruginosa directly utilizes these metabolites in vivo, providing evidence for mucin-based cross-feeding in the progression of lung disease. Finally, a mucin-overproducing cell line was used to assess whether P. aeruginosa colonization of the epithelium was facilitated by mucin degradation. P. aeruginosa showed increased colonization and a heightened immune response (IL-8) when co-seeded with mucin degraders. Together, these data implicate a central role for commensal anaerobes in the colonization of the airways by P. aeruginosa,

and motivate future studies targeting bacterial mucin fermentation as a potential therapeutic intervention for P. aeruginosa airway infections.

Intestinal Microbiota Influence Thymic Development in Neonates

Nitya Jain, Brian Seed, Maria Ennamorati, Kara Clerkin, Stefan Halvorsen, Kaitlin Berry, Caryn Porter, Huajun Wang, Vladimir Yeliseyev, Meredith Weglarz, Lynn Bry, Slim Sassi

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Mammalian intestinal microbial communities harbor both an enormous source of commensals as well as potential pathogens. In the postnatal period, the immune system must rapidly develop a discrimination of microbial friend from foe akin to that of self-non-self recognition. Lymphocytes of the T cell lineage that participate in this mucosal process develop in the thymus. We show here that thymic development is influenced by the intestinal microbiota, and that plasmacytoid dendritic cells (PDCs) are one class of antigen presenting cell that transit from the intestine to the thymus during the postnatal period. Experimental perturbation of bacteria and PDCs produces changes in the thymic distribution and residency of PLZF+ innate-like cells. Thus, PDCs may act as sensors of intestinal microbial status that convey compartment information to the thymus to promote appropriate immune responses to the microbiota.

HIV Exposure and Gut Microbiota in South African Infants

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HIV-exposed uninfected infants (HEU) have higher morbidity and mortality and altered immunity compared to HIV unexposed (HU) infants. The gut microbiome is crucial for immune development. Infant microbiota is shaped by maternal factors and diet. HIV-infected mothers may have altered gut, vaginal, and breastmilk microbiota. HEU also initiate prophylactic antibiotics at 6 weeks of age.

Term, vaginally delivered, South African HEU and HU infants were recruited at birth, and followed until 36 weeks. Stool microbial DNA was extracted and the V6 region of the 16S rRNA gene was Illumina sequenced. Data was pre-processed using QIIME and UPARSE, and downstream analyses performed using Phyloseq and metagenomeSeq R packages.

There were no significant difference in alpha diversity between HEU and HU at any time point. However, significant differences in beta diversity were evident at birth, before feeding practices were established (Adonis p=0.001). This difference was no longer evident at 1 week, after breastfeeding was introduced (Adonis p=0.383). At birth, HEU stool was enriched in the taxa Klebsiella and Blautia and deficient in Erysipelotrichaceae.

Maternal HIV infection during gestation or delivery profoundly alters gut microbial makeup, before feeding is introduced.

Analysis of Niche-Specific Adaptations of Vaginal Bifidobacterium spp. Leveraged by Longitudinal Datasets

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Bifidobacterium species are key players in early infant gut development via transmission from maternal body sites and the environment. However, most of what is currently known about Bifidobacterium species comes from the studies of gut isolates. Thus, we sought to elucidate the role of Bifidobacterium species in the vaginal microbiome. Through a 16S rRNA study of ~6,000 samples from the women who participated in the Vaginal Human Microbiome Project (VaHMP) at VCU and ~185,000 samples through the Multi-Omic Microbiome Study-Pregnancy Initiative (MOMS-PI) pregnant cohort, we identified a rare vagitype dominated by Bifidobacterium species, which exhibited stability over time. The most common species observed were Bifidobacterium breve and Bifidobacterium longum subspecies infantis, which have been previously reported to be the most dominant taxa of the infant gut microbiome. Following this observation, we isolated 10 strains of Bifidobacterium breve from samples exhibiting that vagitype and performed bacterial whole genome sequencing. Comparative genomic analyses showed that while most genes were conserved across all B. breve niche strains, the vaginal isolates exhibited differences in predicted carbohydrate and sulfur metabolism, membrane transport and mobile elements compared to gut isolates. These differences may reflect mechanisms of adaptation to the vaginal environment and modulation of the microbiome. This work informs our ongoing investigations of Bifidobacterium strain variation among maternal vaginal, maternal rectal and infant stool samples.

Human Derived Gut Microbiota Modulates Colonic Secretion in Mice by Regulating 5-HT3 Receptor Expression via Production of Acetate

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We have shown that human gut microbiota increases biosynthesis of host serotonin (5-HT), an important neurotransmitter that increases intestinal secretion. In this study we investigated whether gut microbiota modulates 5-HT3R expression and host secretory response to 5-HT.

Methods: We used proximal colon mucosa-submucosa preparations from germ free (GF) and humanized (ex-GF colonized with human bacteria for 4 weeks; HM) mice for Ussing chamber studies and determined change in short circuit current (ΔIsc) in response to 5-HT (0.003-300μM) with or without ondansetron. Receptor expression was quantified using rt-PCR (normalized to L32) and western blot (normalized to GAPDH). Differences between groups were tested using either t-test or ANOVA with P-value lower than 0.05 considered significant. **Results:** 5-HT induced ΔIsc was significantly higher in GF than HM mice. To determine if this was due to an alteration in 5-HTR, we quantified receptor expression and found significantly higher 5-HT3R mRNA and protein expression in GF tissues compared to HM tissues. To determine the microbial mediators that affect expression of 5HT3R, we developed organoids from GF mouse colon and found a significant decrease in 5-HT3R mRNA after application of 10mM acetate. Ondansetron (blocks epithelial and neuronal 5HT3R) significantly blocked 5-HT induced maximum ΔIsc in GF mice but not HM mice. TTX (500 nM; blocks neuronal transmission) had no effect of ondansetron inhibition of 5-HT-induced ΔIsc, suggesting a primary effect on epithelial 5HT3R.

Conclusion: Gut microbial colonization modulate intestinal secretion by downregulating epithelial 5-HT3R expression via acetate production and decreasing host secretory response to 5-HT.

Airway Colonization Induces Th17 Responses in the Lungs and Modulates Allergic Airway Sensitization in Mouse Model of Asthma

Natalia Jaeger, Ryan McDonough, Andrew Kau, Jiani Chai, Chyi Hsieh

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Asthma is a common immune disorder caused by allergic sensitization leading to airway inflammation and obstruction. Previous work has demonstrated that individuals with asthma harbor an altered consortium of microbes within their lungs that is thought to contribute to allergic airway pathogenesis. While investigating the role of airway microbes in a mouse model of asthma, we found that many animals were colonized with Bordetella pseudohinzii, a newly described non-classical bordetella species. We found that inoculation of B. pseudohinzii into mice resulted in long-term colonization of the lungs and upper respiratory tract but did not cause weight loss, pneumonia or other apparent symptoms. Immunologic phenotyping of colonized mice showed that B. pseudohinzii induced the differentiation of antigen specific Th17 cells. This response was primarily detected in the lungs but also the spleens of colonized animals. Inducing allergic airway inflammation in colonized mice resulted in an altered allergic response characterized by decreased eosinophilic inflammation. Together, these results imply an important role for bacterial airway colonization in modulating immune responses in the lung.

Microbial Delivery of Antimicrobial Peptides for Protection Against Multidrug-Resistant Pathogens

Yiannis Kaznessis, Kathryn Geldart, Brittany Forkus, Gary Dunny, Sushma Kommineni, Nita Salzman

University of Minnesota

Numerous probiotic bacterial species are known to produce antimicrobial peptides (AMPs) targeting different pathogens of interest, but native peptide expression is often low or induced under uncontrollable conditions, making these probiotics therapeutically unreliable.

We harness this natural defense mechanism for the treatment of intestinal infections by engineering probiotic bacteria that can be orally administered and will reliably express and secrete AMPs targeting the pathogen of interest in the intestines. We develop libraries of probiotic species, promoters, secretion systems, and AMPs to enable rapid development of new probiotics targeting a wide array of pathogens.

In this presentation, we will discuss probiotic E. coli Nissle 1917 (EcN) engineered to deliver AMPs targeting vancomycin-resistant Enterococcus (VRE), an opportunistic pathogen that causes thousands of hospital-acquired infections and deaths each year.

We first demonstrate the ability of the probiotic to reduce VRE counts in laboratory cultures. Modified EcN eliminates over 99% of VR E. faecium after one hour of co-culture.

We then test the efficacy of our probiotics in reducing intestinal pathogen counts in mice colonized with VRE via oral administration. Mice administered EcN producing AMPs on average exhibited a 10x reduction in E. faecium counts compared to mice administered unmodified probiotic.

We demonstrate that this EcN probiotic platform can be readily modified to express alternative peptides targeting a variety of pathogens. Additionally, unlike broad-spectrum antibiotics, the AMPs expressed by these microbes offer species-specific activity. This specificity reduces pressure for resistance development.

Nasal Microbiome Features of Staphylococcus Aureus Colonization and Infection During Critical Illness

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Background: Intranasal colonization with Staphylococcus aureus (SA) is a risk factor for nosocomial SA infection. We evaluated the bacterial community features associated with SA colonization and infection in a cohort of critically ill subjects at high risk for nosocomial SA infection. **Methods:** We enrolled a discovery cohort (15 intubated subjects) and a validation cohort (65 intubated subjects) from a medical intensive care unit at an academic medical center. Flocked swab samples from the anterior nares were collected at 24-48 hour intervals for the duration of intubation. We performed Illumina MiSeq sequencing of the amplified V1-V2 hypervariable region of the 16S rRNA gene, clustered operational taxonomic units (OTUs) at 97% sequence similarity, and assigned taxonomy using BLAST against the Living Tree Project database. **Results:** 42 specimens were collected from the discovery cohort; 157 specimens were collected from the validation cohort. The most commonly observed species were Staphylococcus epidermidis, Corynebacterium tuberculostearicum, Corynebacterium propinquum, Propionibacterium acnes, and SA. Principal coordinate analysis of pairwise unweighted Jaccard distances revealed clustering of SA-positive samples. Corynebacterium tuberculostearicum was most strongly associated with the absence of SA infection ($p < 0.001$). **Conclusions:** The presence of Corynebacterium tuberculostearicum in the anterior nares bacterial community is associated with lower risk of SA infection.

Gut Microbial Metabolites Fuel Host Antibody Responses

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Antibody production is a metabolically demanding process that is regulated by gut microbiota, but the microbial products supporting B cell responses remain incompletely identified. We report that short-chain fatty acids (SCFAs), produced by gut microbiota as fermentation products of dietary fiber, support host antibody responses. In B cells, SCFAs increase acetyl-CoA and regulate metabolic sensors to increase oxidative phosphorylation, glycolysis, and fatty acid synthesis, which produce energy and building blocks supporting antibody production. In parallel, SCFAs control gene expression to express molecules necessary for plasma B cell differentiation. Mice with low SCFA production due to reduced dietary fiber consumption or microbial insufficiency are defective in homeostatic and pathogen-specific antibody responses, resulting in greater pathogen susceptibility. However, SCFA or dietary fiber intake

restores this immune deficiency. This B cell-helping function of SCFAs is detected from the intestines to systemic tissues and conserved among mouse and human B cells, highlighting its importance.

Probiotic Use of Women Followed for Gut Microbial Composition in Relation to Perinatal Mood and Anxiety Disorders

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Objective: While gut microbial composition changes over pregnancy and microbial composition has been linked to depression and anxiety, the microbiota-gut-brain axis has not been studied in relation to Perinatal Mood and Anxiety Disorders (PMAD). Women desire dietary interventions such probiotics to prevent development of PMAD, but there is limited data. **Methods:** Thirty women, recruited in the 1st or 2nd trimester through flyers, the web and word of mouth, were given the SCID-IV to determine current and past psychiatric disorders. Women with bipolar or psychotic disorders were excluded. Subjects were asked about consumption of probiotic containing foods and pills. **Results:** Almost half had a current psychiatric diagnosis (majority with an anxiety disorder). 24 had a past psychiatric diagnosis including 40% with a history of Major Depression and 23% with a history of PTSD. Half of the subjects were classified as high consumers of probiotics (i.e., consume yogurt daily and/or consume kefir, kombucha, sauerkraut or miso on a regular basis and/or take a probiotic pill). 7 in the high consumers had a current diagnosis and 8 in the low consumers had a current diagnosis. When the last person delivers in July, fecal samples from two points in pregnancy and one postpartum for all subjects will be analyzed for microbial composition. **Conclusions:** There was no significant difference whether the subject was a high consumer of probiotics or not and whether she had a current psychiatric diagnosis. This study provided information for more systematically assessing probiotic consumption in future studies. However this may indicate other factors will be more important for understanding the microbiota-gut-brain axis and PMAD.

Vaginal Bacteria Modify HIV Tenofovir Microbicide Efficacy in African Women

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Microbicide-based pre-exposure prophylaxis (PrEP) to prevent HIV infection has shown inconsistent results in women. We investigated whether the vaginal microbiome modulated topical microbicide efficacy in the CAPRISA 004 tenofovir gel trial. Two major bacterial community state-types were

identified in the 688 women profiled; one of low diversity where Lactobacillus iners and crispatus were the most common (Lactobacillus-dominant (LD), 59.2%), and the other with high ecological diversity where Gardnerella vaginalis predominated, co-dominant with Prevotella, Mobiluncus, and other anaerobic bacteria (non-Lactobacillus-dominant (non-LD), 40.8%). Women with LD had three-fold higher protection than women with non-LD; HIV incidence rates in the tenofovir and placebo gel arms were 2.7 and 6.9 per 100 women-years in LD women (Incidence rate ratio (IRR)=0.39 (95% Confidence Interval) (CI) 0.16, 0.89, P=0.013), compared to 6.4 and 7.8 per 100 women-years in non-LD women, respectively (IRR=0.82; CI: 0.37,1.77; P=0.644). Detectible mucosal tenofovir was considerably lower in non-LD women (P=0.008), despite similar adherence, and negatively correlated with G. vaginalis abundance and other anaerobic bacteria. Bacterial cultures demonstrated that tenofovir is rapidly metabolized and depleted by G. vaginalis, and other anaerobic bacteria. Our study provides new evidence linking vaginal bacteria to microbicide efficacy in women, and proposes a putative mechanism of tenofovir depletion via metabolism by bacteria, which may be a factor contributing to the variable effectiveness of topical tenofovir-containing microbicides.

Exposure to Luminal Antigens in Early Life Is Controlled for the Promotion of Tolerance to the Microbiota

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It has been observed early life is an important time for the development of tolerogenic responses. This time is also correlated to the establishment of the intestinal microbiota, which is also necessary for the development of tolerance. However, it is unclear why tolerance is established best during early life and how the microbiota confers an effect on the immune system. We identified a pre-weaning interval in which gut luminal antigens, including those from the microbiota, are shunted to the colonic immune system to induce the development of RORγt+ inducible regulatory T cells (iTregs) and enhanced tolerance towards both dietary antigens and the commensal microbiota. Luminal antigen delivery in early life was mediated by the formation of goblet cell-associated antigen passages (GAPs), which were regulated by goblet cell intrinsic sensing of breast milk derived epidermal growth factor and the blooming gut microbiota. Disruption of the gut microbiota or GAP formation and antigen delivery during early life resulted in abrogation of tolerance to dietary antigens encountered during this time, a long-lived decrease in RORγt+ iTregs, and skewing of the immune system toward systemic allergic Th2 responses. We propose the microbiota, along with maternal factors, control both antigen delivery and the induction of RORγt+ iTregs during early life facilitating enhanced tolerance to dietary and microbial antigens encountered during this time and allowing development of a balanced and durable immune system necessary to suppress inappropriate responses.

Roux-en-Y Gastric Bypass Surgery Shifts Gut Microbial Communities and Associated Metabolites

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Drastic physiological changes happen after bariatric surgeries, specifically Roux-en-Y Gastric Bypass (RYGB), these changes lead to environmental changes that craft the gut microbiome. Changes in gut microbiome after RYGB have been associated with weight loss and diabetes remission in humans. Microorganisms produce a variety of metabolites that enhance host-microbe communication; these molecules vary from fermentation end products such as short chain fatty acids (SCFAs) to secondary bile acids. SCFAs, butyrate, and propionate, increase in concentrations after RYGB surgery and are known to induce satiety in animals due to their affinity to free fatty acid receptors. RYGB surgery also increases the abundance of amino acid degradation genes, although the metabolic products have not been identified or quantified in humans yet. In a longitudinal study, my research group is investigating microbial and metabolic changes after RYGB surgery and comparing findings with cross-sectional studies. Microbiome and metabolic changes seem long lasting and associated with weight-loss after RYGB. Careful analysis of our wide range of genomic and metabolic data will help uncover possible mechanisms for the hypothesized role of the gut microbiome and successful weight loss after RYGB, this ultimately can lead to microbiome targeted non-surgical therapies.

Lactobacillus-Deficient Cervicovaginal Bacterial Communities Are Associated With Increased HIV Acquisition in Young South African Women

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The female genital tract (FGT) plays a critical role in the acquisition of HIV infection in women. Although the majority of new infections globally occur in women following HIV passage across the FGT, we do not fully understand the mucosal factors that affect susceptibility. Elevated inflammation in the FGT is associated with increased HIV risk. Cervicovaginal bacteria modulate genital inflammation, however their role in HIV susceptibility has not been elucidated. In a prospective cohort of young, healthy South African women, we found that individuals with diverse genital bacterial communities dominated by anaerobes other than Gardnerella were at over 4-fold higher risk of acquiring HIV and had increased numbers of activated mucosal CD4+ T cells compared to those with Lactobacillus crispatus-dominant communities. We identified specific bacterial taxa linked with reduced (L. crispatus) or elevated (Prevotella, Sneathia, and other anaerobes) inflammation and HIV infection and found that high-risk bacteria increased numbers of activated genital CD4+ T cells in a murine model. We used single cell RNAseq to identify specific host responses involved in the generation of genital inflammation by high risk bacterial communities. Our results suggest that highly prevalent genital bacteria increase HIV risk by inducing mucosal HIV target cells. These findings may be leveraged to reduce HIV acquisition in women living in sub-Saharan Africa.

Transcriptomic Profile of the Caenorhabditis Elegans Intestinal Bacteria

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Gut bacteria impact many essential functions in any host organisms, ranging from the regulation of nutrient resources and mobilization, animal development, and immune responses amongst others. Recently, the nematode Caenorhabditis elegans has become an advantageous model organism to better understand how bacteria, and its metabolic and gene regulatory networks, regulate host physiology. In particular, metabolites from bacteria alter development, lifespan, and pathogen resistance in worms. The ability to use high-throughput sequencing to identify different bacterial communities in varying host genotypes has increased our knowledge of host-bacteria interspecies interactions. However, less is known regarding the transcriptional profile of the bacteria in the worm; specifically, how does the transcriptional profile change with host genotype? To better examine this, we developed an RNAseq protocol and bioinformatics pipeline to elucidate bacterial gene expression differences in known models of aging. Briefly, RNA extracts (n=18) were subject to ribosomal RNA subtraction, cDNA synthesis, Nextera library preparation and sequencing using the Illumina Hiseq platform. Our bioinformatics pipeline utilizes the most robust programs for quality filtering, assembly, annotation, differential gene analysis. Preliminary bacterial transcriptome data indicate differences in bacterial expression of several biosynthetic pathways and virulence mechanisms which may contribute to the aging phenotypes of the long-lived daf-2/InsR mutant and the short-lived daf-16/FOXO transcription factor mutant. These studies will help further identify interspecies interactions that modify host physiology.

Gut Microbial Dysbiosis and Post-Transplant Complications in Kidney Transplant Recipients

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Gut microbial dysbiosis has been linked to infectious and immunological complications in recipients of stem cell or organ transplantation. We investigated the relationship between the gut microbiota and post-transplant complications: (1) diarrhea; and (2) urinary tract infections (UTI). We prospectively recruited 71 kidney transplant recipients for serial fecal specimens and profiled their gut microbiota using 16S rRNA deep sequencing of the V4-V5 region. Twenty-four subjects developed post-transplant diarrhea with 18 subjects providing 29 fecal samples at the time of diarrhea (N=29, Diarrheal Specimens) while 47 subjects did not develop diarrhea in the first 3 months of transplantation and provided 119 fecal samples (N=119, No Diarrheal Specimens). Compared to No Diarrheal Specimens, the Diarrheal Specimens had a lower Shannon diversity index ($P<0.001$) and had lower abundances of 13 commensal bacterial genera (FDR<0.15). Within the Diarrheal Specimens, 93% were negative for bacterial, parasitic, and viral diarrheal-associated pathogens when evaluated using the FilmArray GI Panel PCR assay. Among the 71 subjects, 13 developed Gram-negative UTIs with 9 subjects providing 11 fecal samples at the time of UTI (N=11, UTI-associated Specimens) while 58 subjects did not develop UTI in the first 3 months of transplantation and provided 135 fecal samples (N=135, No UTI-associated Specimens). The UTI-associated Specimens had significantly higher fecal Proteobacteria abundance than the No UTI-

associated Specimens (P<0.05). Our identification that post-transplant diarrhea and UTI are associated with gut dysbioses suggests targeting the gut microbiota may be of value in preventing and/or treating these complications.

Commensal Corynebacterium Shifts Staphylococcus Aureus Toward Commensalism by Quenching Quorum Sensing

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The interactions between humans and their microbiota range along the continuum from commensalism to pathogenesis. In some cases, the same bacterial species that colonize humans asymptomatically also cause severe infections. Key factors in modulating these interactions appear to include host and bacterial genetics and the microbiota composition, but precise relationships remain unclear. We have evidence that virulence of Staphylococcus aureus, a clinically significant human pathogen, is limited by coresidency with commensal Corynebacterium species. S. aureus resides in the nostril and skin microbiota of up to 25% of humans, often with Corynebacterium, e.g., the common human skin commensal Corynebacterium striatum. S. aureus virulence can be triggered by its quorum sensing accessory gene regulator (agr) system, allowing transition between commensal and pathogenic states. We found that S. aureus responds to coculture with C. striatum with decreased expression of agr-induced virulence genes and increased expression of agr-repressed genes encoding surface-associated proteins. Among the S. aureus genes exhibiting increased expression in the presence of C. striatum are a number of genes reportedly expressed during nasal colonization. Consistent with this, exposure to cell-free conditioned medium from C. striatum, S. aureus exhibited decreased hemolysin activity and increased epithelial cell adhesion. Finally, in a murine subcutaneous abscess infection model, S. aureus populations were reduced by coinfection with C. striatum, whereas C. striatum numbers expanded. These data are consistent with a model in which S. aureus responds to commensal Corynebacterium species by limiting virulence and shifting toward a commensal state.

Dissecting the Human Skin Microbiome in Health and Disease – From Strain-Level Composition to Transcriptional and Metabolic Activities in the Host Environment

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The human skin microbiome plays important roles in skin health and disease. However, bacterial population structure and diversity at the strain level, as well as the underlying molecular mechanisms of the microbiome in health and disease pathogenesis are often poorly understood. Using acne as a disease model, we aim to understand the skin microbiome at the strain level and at the transcriptional and metabolic levels in response to host metabolism. Our metagenomic analysis demonstrated that the strain population structures of Propionibacterium acnes, a major skin commensal, were significantly different between acne and healthy individuals. Certain strains were highly associated with acne while other strains were enriched in healthy skin. By metatranscriptomic analysis, we found that the transcriptional profiles of the skin microbiota of acne patients were distinct from healthy individuals.

The vitamin B12 biosynthesis pathway in P. acnes was significantly down-regulated in acne patients. We further revealed that vitamin B12 level modulates the production of porphyrins, a group of proinflammatory metabolites, in P. acnes in a strain-specific manner. Acne-associated type IA-2 strains inherently produce significantly higher levels of porphyrins, which were further enhanced by vitamin B12 supplementation. On the other hand, health-associated type II strains produced low levels of porphyrins and did not respond to vitamin B12. Our studies demonstrated a new paradigm of the strain composition and metabolic activities of the skin microbiome that could explain disease pathogenesis and provided evidence that metabolite-mediated interactions between the host and the skin microbiota play essential roles in disease development.

Role of the Human Virome in Kidney Transplant Disease

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The tenuous balance between health and disease is influenced by the interplay between the human virome and host immune functions. This is particularly important in the setting of vulnerable host immune states such as immunosuppression in solid organ transplant recipients. We found that alterations in the circulatory (plasma) virome in kidney transplant recipients were associated with progression towards BK polyomavirus-associated nephropathy (BKVAN) in a manner that reversed when immunosuppression was reduced. We demonstrate that the urinary virome harbors a distinct community of viruses that undergoes significant disease-specific contractions. We show that healthy individuals also harbor a complex urinary virome, indicating that it is not a transplant-limited artifact. Together, our data has two broad implications. First, immunosuppression-mediated virome alterations may contribute to transplant disease. Second, host functional immunocompetence can be defined by virome/microbiome terms.

Resetting Gut Microbiota by Lactobacillus Reuteri DSM 17938 Inhibits Treg-Deficiency-Induced Autoimmunity (IPEX Syndrome) Via Adenosine 2A Receptors

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Regulatory T-cell (Treg) deficiency causes lethal, CD4+T cell-driven autoimmune diseases. Stem cell transplantation is used to treat these diseases, but this procedure is limited by the availability of a suitable donor. The intestinal microbiota drives host immune homeostasis by regulating the development of Treg, TH1 and TH2 cells. It is currently unclear if Treg-deficiency autoimmune disorders can be treated by targeting the enteric microbiota. Our aims are to determine the autoimmunity, gut microbiota, and plasma metabolomics affected by probiotic Lactobacillus reuteri DSM 17938 (LR), and to further identify the mechanism of modulated metabolite(s) in suppressing autoimmunity in Treg-deficient scurfy (SF) mice. We demonstrated that Foxp3+Treg deficiency results in gut microbial dysbiosis and autoimmunity over the lifespan of SF mouse. Remodeling microbiota with LR prolonged survival and reduced multi-organ inflammation in SF mice. LR changed the metabolomics profile disrupted by Treg-deficiency with a major effect of restoring levels of the purine metabolite inosine. Feeding inosine itself prolonged life and inhibited multi-organ inflammation by reducing TH1/TH2 cells

and their associated cytokines. Mechanistically, the inhibition of inosine on the differentiation of TH1 and TH2 cells in vitro depended on adenosine A2A receptors. Both A2A receptor specific antagonist or genetically knockout A2A to SF mice reversed the anti-inflammatory effects of both inosine and LR in vivo. In conclusions, A2A receptors mediate a substantial protective effect of inosine and LR. The LR-modulated-microbiota-inosine-A2A axis might represent a potential avenue for combatting autoimmune diseases mediated by Treg dysfunction.

Niche-Association and Retention Dynamics in the Human Microbiome

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The NIH Human Microbiome Project (HMP) has provided one of the broadest characterizations of the baseline human microbiome, and it has served as a reference in studies of disease, microbial population diversity, biogeography, and molecular function. Here, we present new findings and a dramatic expansion of shotgun metagenomes (now ~2,400 samples) from the HMP, termed HMP1-II, with three new characterizations of microbial health: functional specialization, strain distributions, and temporal dynamics. Species-level functional characterization showed different taxa contributing common functions at different body sites, as well as newly defining niche- and human-specific microbial metabolism and signaling. Strain identification revealed distinct subspecies clades for some species, some of which showed evidence of strain-level specialization to specific body sites. Temporal analysis using Gaussian processes decomposed microbial and functional variation by their characteristic rates of change within and among individuals. Species dynamics in the gut were most individualized, for example, while pathway abundances rarely were. By identifying features which structurally and dynamically maintain differences between individuals, we have achieved an improved understanding of personalized human microbiome strain-level structure and function.

Clostridiales Correlate With Intestinal Barrier Maturation in Preterm Infants

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Intestinal barrier immaturity, or “leaky gut,” is the proximate cause of susceptibility to necrotizing enterocolitis in preterm neonates. The impact of the intestinal microbiota development on intestinal mucosal barrier integrity has not yet been evaluated. In this study, we investigated a longitudinally sampled cohort of 38 preterm infants with gestational age <33 wk and birthweight <1501 gm during the first two weeks of life. We collected fecal samples to access intestinal microbiome at day 1, 8, and 15, and measured intestinal permeability (IP) by urinary detection of orally administered sugar probes lactulose and rhamnose. Rapid decrease in IP indicating intestinal barrier function maturation correlates with a significant increase in community diversity and alteration in community composition and structure. In particular, increasing abundance of Clostridiales was significantly associated with low IP at

all timepoints. Clostridiales were also associated with neonatal factors previously identified to promote infant intestinal barrier maturation, such as early introduction of breast milk feeding (< day 2), time to full breast milk feeding (<day 10), and shorter period of antibiotic exposure (<4 days). Metagenomic and metatranscriptomic analyses revealed that Clostridiales is highly transcriptionally active and is co-expressed with Bifidobacterium. The results suggest that neonatal factors favor the early colonization of the gut microbiota by members of the Clostridiales which altogether are associated with improved intestinal barrier in preterm infants. The translational aspect of the study could lead to a novel strategy to promote intestinal barrier maturation in preterm infants and potentially lower the risk to NEC.

The Critical Window in Neonatal Microbiome Development: Exposures and Outcomes

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The gut microbiome plays a critical role in nutrient metabolism and immune maturation, and there is emerging evidence of a critical window in neonatal life when the foundation of adaptive and innate immunity is initiated. Perturbation of colonization with keystone taxa during this neonatal window has been shown to increase disease risk, including allergy, atopy, and obesity. Conversely, health promoting microbes offer promise to reducing disease risk, such as type 1 diabetes and asthma. As part of a US prospective study of over 1600 mother-infant dyads, we enroll pregnant women at 24 weeks' gestation, and collect risk factor data (e.g. diet, environmental toxicants) along with biological samples including maternal microbiome samples. At birth, we analyze cord blood (immune profiling, DNA methylation), placental tissue (metals, DNA methylation, gene expression), and serial microbiome and metabolomics samples in infants from birth, 6 weeks, and 1 year. Findings to date include vast differences in microbial succession and associated metabolomics in infants delivered operatively and fed formula in comparison to those delivered vaginally and breastfed. Common protocols of pre-, peri- and postnatal antimicrobials, which result in antibiotic exposure for nearly 30% of women for GBS, and 30% of women for operative prophylaxis, followed by 5-7% of newborns for suspected blood stream infection, result in perturbation of vertical transmission of vaginal and gut microbes to the newborn during this critical window. Our findings suggest that common exposures such as feeding method, mode of delivery, and antimicrobials play substantial roles in the acquisition of keystone taxa during this critical window of immune maturation.

Composition of Vaginal Microbiota During Labor and the Effect of Lubricant Use

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Background: Maternal microbes transferred at birth form the basis of the neonate's microbiome. Vaginal dysbiosis is linked with many biological and behavioral factors, including use of personal lubricants that can alter microbial composition and damage the integrity of vaginal epithelium. Similar lubricants are frequently used during labor, but, the effect of lubricant use on vaginal microbiota during labor has not been studied. **Purpose:** This study aimed to characterize the composition of vaginal microbiota during labor and to investigate the effect of lubricant use on its bacterial composition. **Methods:** Fifteen participants collected mid-vaginal specimens during pregnancy, labor, and in the postpartum period, and clinical labor data were extracted from medical records. 16S rRNA gene profiling

was used for bacterial composition and multiple linear regression was used to investigate the effect of intrapartum lubricant use. **Results:** The composition of vaginal microbiota varied among participants, with a notable high relative abundance of L. iners and G. vaginalis. A significant bivariate negative correlation between lubricant use and relative abundance of L. crispatus disappeared when controlling for time since ruptured membranes. A trend between lubricant use and changes in the composition of vaginal microbiota as measured by the Jensen-Shannon distance was noted but not significant. **Conclusions:** The study offers novel information about the effect of lubricant use on composition of vaginal microbiota. The potential relationship between lubricant use and L. crisptatus has important clinical significance and can be used to build evidence that supports a less invasive approach to perinatal practice.

Gut Microbiota and Cardiovascular Disease (CVD) Risk Factors: Early Results from the CARDIA (Coronary Artery Risk Development in Young Adults) Microbiome Study

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Background: The gut microbiota has emerged as a novel risk factor for CVD, but there is a lack of population-based epidemiologic data with which to confirm biologic pathways and public health relevance. The CARDIA Microbiome Study was initiated to quantify associations between gut microbial measures and CVD in an ongoing U.S. cohort of black and white adults. **Methods:** Participants (n=612) were from CARDIA participants who attended the Year 30 follow-up examination (2015-16) and who completed a home stool collection. The 16S rRNA marker gene (V3-V4) was sequenced using Illumina MiSeq (2x300). Ribosomal Database Project (RDP) tools were used to classify and assign taxonomic groups. Diversity measures and Principal Coordinates Analysis (PCoA) scores were derived from tables of taxonomic abundance. Regression was used to quantify associations between microbial measures and CVD risk factors with false discovery rate (FDR) adjustment. **Results**: In preliminary analysis, we observed significant differences in microbial composition by race, with significant dissimilarity based on principal coordinate analysis. The Framingham Risk Score (a summary measure of CVD risk) was positively associated with 4 genera, including *Prevotella* and *Allisonella*. Systolic blood pressure was significantly associated with 25 genera, including *Akkermansia (inverse), Prevotella (positive), and Catenibacterium (positive).* **Conclusions:** The CARDIA Microbiome Study provides a unique resource for understanding the role of gut microbiota with respect to CVD risk in a population-based biracial cohort. Early analysis reveals significant differences in gut microbial composition according to race and CVD risk factors. Future work will further define gut microbiota profiles that may contribute to CVD risk.

Fecal Microbiota Transplantation in Children Does not Significantly Alter Body Mass Index

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Fecal microbiota transplantation (FMT) is a promising therapy for Clostridium difficile infection (CDI) and a potential treatment for ulcerative colitis (UC). Limited data confirm safety. However, it is still unclear whether the changes in intestinal microbiome will affect energy homeostasis or metabolism. Animal studies clearly demonstrate that obesity can be transmitted through the microbiome. FMT from nonideal donor was found to induce excessive weight gain in a case report. This brings an intriguing question whether FMT from healthy donors affects recipient's body mass index (BMI). In our randomized placebo-controlled pilot study children patients with CDI (n=8) or UC (n=12) were randomly divided into control and FMT groups. The BMI was recorded pre-FMT, 1, 3, 6, and 12 months post-transplantation. The age range of Clostridium difficile infection cohort was 1-17 years (average 8.5 years), while the range was 8-21 years for ulcerative colitis cohort (average 15.2 years). Though the sample size was limited for both groups in our study, we successfully found that the BMI percentile was changed by (-0.7), (-1.8), 1.3, 4.6 (%tile) in Clostridium difficile infection, while by 3.6, (-3.3), 3.7, 7.1 (%tile) in ulcerative colitis at 1, 3, 6, and12 months after FMT. The changes were not significant compared to control groups ($p > 0.05$). We conclude that FMT from healthy donors does not significantly alter body mass index in children with Clostridium difficile infection and ulcerative colitis over 12 months. Future research will focus on enhancing the study by increasing the cohort size, and minimizing the effects of confounding variables including the medications or the severity of disease.

Maternal High-Fat Diet Results in Microbiota-Dependent Expansion of Type 3 Innate Lymphoid Cells (ILC3s) and Susceptibility to Inflammation in Neonatal Mice

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The average American diet is dominated by high-fat foods and over 50% of women of childbearing age are either obese or overweight. High fat diet (HFD) in adults is associated with an altered fecal microbiota. While perinatal complications have been described, long-term outcomes for offspring are unknown.

Objective: To determine the effect of maternal HFD on acquisition of the microbiota and susceptibility to inflammation in offspring. **Methods:** qRT-PCR and next-generation sequencing of bacterial 16S rRNA genes in colonic fecal contents from HFD and Regular diet (RD) pups. qRT-PCR and ELISA of whole intestine were used to profile cytokine expression and production. Flow-cytometry of lamina propria (LP) cells to characterize cell populations. Microbiologically sterile (GF) pups were colonized with HFD or RD microbiota and flow cytometry performed. Susceptibility to intestinal injury was examined using the LPS/PAF model. **Results:** 1-, 2- and 3- week-old pups of mothers on HFD had a unique microbiota that was dominant in Firmicutes. Cytokine profiling revealed increased production and expression of inflammatory cytokines, with markedly increased IL-17. Flow cytometry revealed a unique population of cells in the LP producing IL-17, which were identified as ILC3s. Colonization with HFD microbiota alone, in GF mice, resulted in recapitulation of the HFD WT phenotype. There was increased susceptibility to the LPS/PAF model of intestinal injury in HFD pups that was significantly reduced when IL-17 was blocked. **Conclusion:** HFD offspring have an altered microbiota marked by an increase in Firmicutes,

which promotes the expansion of IL-17 producing ILC3s. Blocking IL-17 rescues HFD pups from LPS/PAF induced intestinal injury.

Effects of Infant Diet on the Developing Gut Resistome

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Introduction: Pediatric gut microbiota are a reservoir of antibiotic resistance genes. Our prior work shows that gut-associated resistance genes (resistome) in young infants differs from those of their mothers, even in without antibiotic exposure. We hypothesize that young infants' diet influences the development of the resistome in early life. **Methods:** We selected 60 healthy twins who had not been exposed to antibiotics in the first week of life, and whose stools had been collected at monthly intervals for a prior study. For each subject, we prepared every available stool sample from birth to 8 months of age for whole-metagenome shotgun sequencing (N=448 samples). **Results/Discussion:** Study infants were born at a median of 37 weeks completed gestation (IQR 1wk), median birthweight was 2735g (IQR 535g). 56% of the infants were born via Caesarian section, and 44% were delivered vaginally. Three infants received feeds via nasogastric tube while in the nursery; the remainder were only fed by mouth. 18% of the infants were exclusively breastfed in the hospital, 55% were fed both breastmilk and formula in the hospital, and 27% were exclusively formula fed. During the study period, these infants underwent 183 feeding transitions between birth and the age of 8 months (15 breastfeeding to mixed breast/formula, 10 breastfeeding to formula, 6 mixed breastfeeding/formula to breastfeeding, 57 mixed breastfeeding/formula to formula, 8 formula to breastfeeding, 22 formula to mixed breast/formula, 3 formula to cow's milk, 2 cow's milk to formula, and 60 initiations of solid food). Analysis of short-read whole-metagenome sequence data using a mixed model to quantify the effects of feeding transitions on the resistome is ongoing.

High Pulmonary Arterial Pressures Are Associated With Decreased Oral Microbial Nitrate Metabolism in the Mouth

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Background: Impaired signaling and production of nitric oxide (NO) are hallmarks of pulmonary hypertension (PH). Dietary nitrate and nitrite serve as NO donors, but bioactivation of nitrate in mammals requires unique bacterial nitrate reductase enzymes (NRs) from commensal oral bacteria. We investigated the relationship of oral bacterial nitrate metabolism and PH. **Methods:** We performed bacterial 16S ribosomal RNA sequencing and quantification using Illumina MiSeq in oral wash (OW) from patients undergoing right heart catheterization. Sequencing data were processed with Qiime and PICRUSt. Oral nitrate reductase enzyme activity was measured via an in vitro reaction with nitrate under anoxia and normalized to 16S content. Non-parametric p-values with FDR correction are presented. **Results:** 65 participants were included (43 with PH, 22 controls). We identified a ratio of bacterial taxa (NR Index) comprised of 3 bacteria most strongly (Rothia, Veillonella, Lactobacillus) and 3 most negatively (Fusobacterium, unidentified Neisseriaceae, Porphyromonas) associated with predicted nitrate reduction via PICRUSt. We verified that this ratio reflected actual nitrate reducing capacity by directly measuring oral wash nitrate reduction in vitro (p=0.004). Finally, we examined the relationship

between the NR Index and PH diagnosis and mean PA pressure (mPAP) as a measure of PH severity. The NR Index was reduced in individuals with PH (p=0.004), and there was an inverse relationship between mPAP and the NR Index (p=0.007). **Conclusions:** PH and PH severity are associated with a reduction in both predicted and measured oral microbial NR activity and a decrease in the ratio of high to low nitrate reducing oral bacteria.

Control of Epithelial Homeostasis by the Microbiota

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The resident prokaryotic microbiota of the intestine can influence normal gut proliferation, development and wound healing. We describe a common paradigm wherein contact of prokaryotic organisms stimulate the enzymatic generation of reactive oxygen species (ROS) in the host epithelia. These events occur via the action of highly conserved NADPH oxidase enzymes (Nox1 in mammals and dNox in Drosophila). Interestingly, a subset of bacterial taxa, predominately Lactobacilli, potently stimulates Nox dependent ROS generation in both systems, and activates redox responsive transcriptional circuits, including the Nrf2/Keap pathway. Germ-free mice and flies exhibit reduced epithelial proliferation and increased sensitivity to injury. Consistently, epithelial-specific Nox1 and Nrf2 null mice, and dNox and CnC (Nrf2 ortholog in flies) mutant Drosophila demonstrate aberrant intestinal stem cell dynamics and responses to injury. Conversely, commensal bacteria such as the Lactobacilli and Akkermansia accelerate epithelial cell movement and mucosal restitution mice and flies, and correct proliferative defects observed in germ-free animals, in a Nox1 and Nrf2 dependent fashion. At the tissue level, bacterially induced ROS generation is strikingly excluded from discrete stem cell niches, resulting in a redox gradient across stem cell compartments in both mice and flies that is absent in germ-free animals. Ectopic generation of ROS in enterocytes outside the stem cell niche phenocopied the effects of the natural microbiota. These data suggest how bacterial symbionts utilize spatially compartmentalized generation of ROS for controlling highly conserved signaling events that regulate intestinal development and homeostasis.

Control of Pathogen Colonization by Host Immunity and the Microbiota in the Gut

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The mechanisms that allow enteric pathogens to colonize the intestine in the presence of the microbiota and how host immunity and the indigenous microbiota inhibit pathogen colonization remain poorly understood. Our laboratory is using *Citrobacter rodentium*, a mouse pathogen that models human infections by enteropathogenic *E. coli*, to understand the mechanisms that regulate the colonization and clearance of the pathogen in the gut. These studies have shown how the pathogen colonizes and replicates successfully early during infection and how host immunity and the indigenous microbiota cooperate to eradicate the pathogen in the later stage of the infection. These studies have also revealed that Clostridia species protect the host from colonization by *C. rodentium* and *Salmonella enterica* in the intestine. The intestine of mice after birth lack protective Clostridia providing a mechanism to account for the increased susceptibility of mice and humans to enteric infection during the neonatal period.

Tumor Necrosis Factor Receptor 2 Restricts Dysbiosis in Colitis

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Background: Inflammatory bowel disease (IBD) afflicts >1.6 million Americans. IBD results from the loss of homeostasis between host immune system and the gut microbiota, ultimately leading to chronic mucosal damage. Anti- tumor necrosis factor (TNF) therapies are a mainstay therapeutic regimen for IBD and yet TNFR2 polymorphisms have been identified in both ulcerative colitis and Crohn's disease patients. We recently showed that TNFR2 restricts CD8+ T cell expansion and protects mice from colitis. Because CD8+ T cells regulate host-microbial interactions at environmental surfaces, we hypothesized that loss of TNFR2 induces dysbiosis. **Methods:** Tnfr2-/- mice were crossed with Il10-/- mice. 16S rRNA sequences were profiled from fecal samples collected from co-housed Il10-/- and Il10-/-Tnfr2-/- littermates at 4, 12, and 20 wks of age. Data were analyzed using QIIME and PICRUSt. The inflammatory potential of Il10-/-Tnfr2-/- gut microbiome was analyzed by transfer of cecal contents from donor mice to wildtype germfree recipients. **Results:** Loss of TNFR2 resulted in an altered colonic microbiome. Operational taxonomic units (OTUs) classified as Bacteroides were enriched (p=0.0041), and Lactobacillus were depleted (p<0.0001). Il10-/-Tnfr2-/--associated cecal microbiome induced colitis and 2-fold expansion of CD8+ T cells in WT recipients after 2 weeks. **Conclusion:** TNFR2 restricts the development of a pro-inflammatory gut microbiome. Il10-/-Tnfr2-/- gut microbiomes are transmissible in vivo. Understanding the specific role of TNFR2 in maintaining gut microbiome homeostasis could lead to refined therapeutic approaches, especially for IBD patients with CD8+ T cell dysfunction.

Circulating Microbiome and Functional Metagenomic Signature Is Associated With Heavy Alcohol Use and Severity of Alcoholic Hepatitis

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Background: Alcoholic hepatitis (AH) is related to heavy drinking (>60 g/day in men and >40 g/day in women) and associated with intestinal microbial dysbiosis. However, the circulating microbiome signature in AH is unknown. **Aims:** To define (1) circulating microbiome in alcoholics [heavy drinking controls (HDC), moderate AH (MAH) and severe AH (SAH)] compared to nonalcoholic controls (NAC); (2) relationship between circulating microbiome and disease severity, and (3) functional relevance of circulating microbiome changes. **Methods:** Four groups (n=76) (1) NAC=20, (2) HDC=19, (3) MAH (MELD ≤ 20, n=18) and (4) SAH (MELD score ≥ 21, n=19) were studied. 16S targeted sequencing of bacterial DNA from whole blood was performed. The linear discriminant analysis (LDA) Effect Size (LEfSe) for across-group differences and PICRUSt for predictive functional metagenomics were used. **Results:** Bacterial DNA in MAH and SAH was significantly higher (p< 0.01). **Circulating Microbiome:** 21 taxa were enriched (LDA score >2) in alcohol groups. Fusobacteria, undetectable in NAC, was significantly enriched in alcohol groups (LDA scores 3.1-4.1) with increment in HDC>MAH>SAH. Bacteriodetes was decreased in HDC, MAH and SAH vs. NAC (p< 0.01). **Relationship To Disease Severity:** Gammaproteobacteria and Betaproteobacteria were inversely related to MELD score (ρ= -0.47 to -0.67, p< 0.05). **Functional**

Metagenomics: SAH had activated type III secretion system and mevalonate pathway of isoprenoid synthesis, and enhanced anthranilate degradation pathway related to biofilm formation. **Conclusions:** Qualitative and quantitative changes in circulating microbiome with shift in metabolic and structural functions are associated with severity of AH.

The Role of Gut Microbiota in Chemotherapy-Induced Behavioral Comorbidities

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Recent evidence indicates that the gut microbiome can influence brain and behavior, including cognition. Approximately one-third of cancer survivors report a cognitive decline after receiving chemotherapy. In addition, many cancer survivors who receive chemotherapy also experience adverse effects on their gut, including diarrhea and vomiting, along with a shift in diversity of their natural gut microbiota. However, very little is known about the potential role of the gut microbiome in the enduring and prevalent consequences of chemotherapy on the brain and behavior (e.g., cognitive impairments). The hypothesis for this study is that chemotherapy shifts diversity in the gut microbiota, which leads to neuroinflammation and cognitive impairments. To test this hypothesis, we injected murine mammary cancer cells into the fourth mammary fat pad in immunocompetent Balb/c female mice. After tumors developed, they were surgically resected. One week after tumor resection, half of the mice received 6 doses of paclitaxel chemotherapy (30 mg/kg; i.p.; every other day); the others received vehicle. After chemotherapy, cognition was tested in all mice using spontaneous alternation, contextual and cued fear conditioning, and novel object recognition tests. Circulating baseline concentrations of corticosterone and cytokines, neuroinflammation, and fecal microbiota were determined. Preliminary data suggest that paclitaxel treatment impaired cued conditioning and increased Gram-negative gut bacteria which were positively related to brain inflammation. By establishing the role of the gut microbiota in the behavioral consequences of cancer potential novel and non-invasive treatment targets may be determined.

Gut Microbiota, Tryptophan Catabolism, and Atherosclerosis in HIV Infection

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Gut microbiota alteration and disturbed tryptophan catabolism have been observed in HIV infection. Among 407 women from the Women's Interagency HIV Study (WIHS) and 339 men from the Multicenter AIDS Cohort Study, we examined associations of plasma tryptophan, kynurenic acid, and kynurenic acid-to-tryptophan (Kyn/Trp) ratio, with incident carotid plaque over 7 years. Bacterial community profiling was performed using 16S rRNA sequencing on stool samples in 150 WIHS women. After adjustment for demographic, behavioral, and traditional CVD factors, plasma tryptophan was significantly associated with decreased risk of incident carotid plaque (RR 0.75 [95% CI 0.64-0.88] per SD), while kynurenic acid (RR 1.34 [1.08-1.65] per SD) and Kyn/Trp ratio (RR 1.41 [1.22-1.64] per SD) were significantly associated with increased risk of incident carotid plaque (all P<0.001). Tryptophan and related metabolites were correlated with specific inflammation/immune activation markers (e.g., soluble CD14, a marker of gut microbial translocation) rather than conventional inflammation markers or CVD risk factors. We

identified that several gut microbes enriched in HIV infection were associated with decreased plasma tryptophan and increased Kyn/Trp ratio. Further bioinformatics analyses revealed bacterial genera that encode enzymes homologous to those involved in human tryptophan catabolism and kynurenine pathway. Our data suggest that disturbed tryptophan catabolism, correlating with specific inflammation and immune activation, might be partly due to HIV-induced gut microbiota dysbiosis, which then leads to increased risk of HIV-related CVD. Gut microbiota might be a modifiable target for the prevention CVD among people with HIV.

TAS2R38 Genotype-Associated Alterations in Sinus Microbiota

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Background: Chronic rhinosinusitis (CRS) is an inflammatory disorder of the airway in which bacteria appear to play a role. The human bitter taste receptor, T2R38, initiates innate mucosal defense systems through detection of bacterial quorum sensing molecules. T2R38 genetics are well-described, and it has been demonstrated that a common polymorphism is associated with the inability to clear Pseudomonas. Clinical study has demonstrated an increase of the "nontaster" haplotype (AVI) in the CRS population, as well as an increase in culture positivity for Pseudomonas. The aim of the current study is to determine if TAS2R38 polymorphisms are associated with alterations in sinus microbiota. **Methods:** Ethmoid sinus samples from CRS patients undergoing surgery were analyzed by 16S rRNA gene sequencing. TAS2R38 genotype was assayed by RFLP. Phylum and genus-level comparisons were made using two-part statistic, ANOVA, and Fisher exact tests. **Results:** 52 patients were included in the study (PAV/PAV = 10, PAV/AVI = 23, AVI/AVI = 19). Phylum-level comparison showed decreased abundance of Proteobacteria (0.04) and increased Bacteroidetes (p=0.03) in PAV/PAV subjects when compared to AVI/AVI (p=0.03 and 0.04, respectively). Genus-level analysis demonstrated increased abundance of B.prevotella (p=0.01) and F.veillonellaceae (p=0.04) in PAV/PAV patients. Pseudomonas was neither less prevalent nor less abundant in the PAV/PAV group. **Conclusion:** TAS2R38 polymorphisms are associated with microbiota alterations in CRS at the phylum and genus levels, however, Pseudomonas did not appear less prevalent or abundant in the PAV/PAV diplotype, suggesting there is a more complex interaction between bitter taste and microbial clearance.

New Insights to the Role of Lactic Acid on the Vaginal Host-Microbe Interaction

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Human vaginal bacterial communities are often dominated by one of four species of Lactobacillus, namely L. crispatus, L. gasseri, L. jensenii or L. iners, which are thought to protect women from bacterial vaginosis, sexually transmitted infections and adverse obstetric outcomes. We have explored interactions between vaginal microbiota and their hosts using multiomics analyses to gain insight to how this is achieved. We have characterized host microRNA expression in vivo and demonstrated that vaginal epithelial cell proliferation is a process controlled by Lactobacillus spp. to maintain host cell homeostasis and provide resistance to Chlamydia trachromatis infections. These findings have been confirmed in vitro using a 3D model of the cervicovaginal epithelium. We have also shown that the D- and L- isomers of lactic acid not only serve to reduce vaginal pH but they also differentially affect the structure of cervicovaginal mucus in a way that prevents C. trachomatis infections, without directly affecting C.

trachomatis. Further, we and collaborator have shown that D-lactic acid down-regulates the production of matrix metalloproteinase (MMP)-8, an enzyme capable of degrading collagen and affecting the integrity of cervicovaginal mucus and the cervical plug that prevents bacteria from entering the upper genital tract during pregnancy. These examples illustrate the power of multiomics analyses of the vaginal microbiome in research done to explore functional interactions between vaginal microbiota and the host with the goal of developing novel approaches to maintaining a healthy and protective vaginal microbiome.

Therapeutic Targeting of the Gut Microbiota

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We seek to understand the molecular mechanisms by which the gut microbiota impact human health. Microbial beta-glucuronidase (GUS) enzymes remove the glucuronic acid sugar linked to a variety of drugs. Gut microbial GUS enzymes, however, cause the acute GI toxicities of many drugs, including cancer chemotherapeutics and non-steroidal anti-inflammatory drugs (NSAIDs). We have discovered and advanced potent, selective and non-lethal inhibitors of microbial GUS enzymes, and have used them to alleviate adverse drug reactions in vivo. Our GUS inhibitors prevent the chemotherapy-induced diarrhea (CID) that is dose-limiting for the anticancer drug irinotecan. CID is a significant unmet medical problem: 70% of chemotherapy patients require dose modification due to CID, 35% require i.v. fluids, and 10% are hospitalized. Using several mouse models of cancer, we show that microbial GUS inhibitors alleviate irinotecan toxicity and dramatically improve irinotecan efficacy. 24 anticancer drugs are known to be glucuronidated, and 21 of those drugs (89%) cause GI toxicity; thus, our approach is likely to find oncology applications well beyond irinotecan. GUS inhibitors also alleviate the small intestinal ulcers caused by NSAIDs. 70% of long-term NSAID users have increased gut permeability, and 30% progress to frank ulcers in the lower GI tract. We have pinpointed the GUS enzymes involved in NSAID and irinotecan reactivation in the Human Microbiome Project gut database. These studies usher in a new era of understanding, and controlling, the actions of key non-mammalian enzymes that crucially affect human health and the treatment of disease.

Longitudinal Dynamics of the Vaginal and Fecal Microbiota During Pregnancy and Gestation at the Onset of Labor

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Reducing preterm birth (PTB) is a global health priority. To meet that goal it is vital to build a clear understanding about the physiologic processes involved in the initiation of labor. Dysbiosis of vaginal microbiota, is a major contributor and ascending infection accounts for 20-40% PTBs. Similarly, the GI microbiota is associated with increased inflammatory signaling essential in labor onset.

The purpose of this study was to examine longitudinal changes in composition and diversity of the vaginal and GI microbiota to establish if interactions between them lead to dysbiotic states that promote labor onset.

In the parent study, a prospective longitudinal design is used to recruit 400 nulliparous women, 12-16 weeks pregnant, aged 18 to 34 with low risk for PTB who are followed to postpartum. Weekly vaginal swabs and monthly stool samples are self-collected. A broad 16S rRNA gene-based metataxonomic characterization of the vaginal and GI microbiota provided composition and taxa relative abundance and diversity was computed with Shannon divergence index.

The PTB rate in the parent study is currently only 5.8% in a population where the rate is 12-16% suggesting that the study itself has become an intervention. This study provides essential data about the relationship between the composition and diversity of vaginal and GI microbiota and gestational length that when combined with changes in diet and behavior from the parent study, could provide insights into why the PTB rate is so low in this cohort. That knowledge is necessary to develop effective clinical interventions to reduce PTB.

Bile Acid C12-hydroxy Epimerization by Human Gut Microbiota

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The gastrointestinal microbiota harbor genes encoding numerous bile acid modifying enzymes. Among these enzymes are hydroxysteroid dehydrogenases (HSDH) which catalyze the reversible NAD(P)(H)-dependent oxidation/reduction of bile acid and steroid hydroxyl groups. While numerous 3α/3-HSDH and 7α/7-HSDH genes have been identified and characterized in numerous gut and soil bacteria, only a single 12α-HSDH has been identified and characterized from Clostridium sp. ATCC 29733. Production of -hydroxy bile acids is associated with decreased toxicity to the host. The 12α-HSDH from Clostridium sp. ATCC 29733 (ERJ00208.1) was searched against the non-redundant protein and nucleotide databases. A phylogenetic tree was constructed using ERJ00208.1, along with a comprehensive tree of known SDR family enzymes. Candidate genes sharing >60% amino acid sequence identity were chosen for cloning and expression, including but not limited to: Clostridium hylemonae TN271 (WP_006441568.1), Eggerthella lenta (CDD59474.1; CDD59473.1; ACV56470.1), Faecalibacterium prausnitzii L2-6 (CBK99423.1). We also identified and expressed genes from two human gut archaea, Methanosphaera stadtmanae DSM 3091 (ABC57112.1) and Methanobrevibacter smithii ATCC 35061 (ABQ87936.1), in E. coli. Clostridium paraputrificum has previously been shown to express 12-HSDH activity. We identified and cloned two SDR-family enzymes in C. paraputrificum encoding putative 12-HSDH. Enzyme kinetic constants and substrate-specificity were determined for the purified recombinant proteins. Reaction product identity was confirmed by UPLC-IT-TOF-MS. Identification of these genes may allow metabolic re-engineering of gut microbial bile acid metabolism as a therapeutic tool.

Grape Proanthocyanidin-Induced Bloom of Gut Microbe Akkermansia Muciniphila Precedes Intestinal Gene Expression Changes Associated With Metabolic Resilience

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Poorly absorbed fruit polyphenols are associated with metabolic resilience raising questions about their mechanisms of action. We previously demonstrated that C57BL/6 mice fed high-fat diet supplemented with grape polyphenols (GP) for 12 weeks resulted in a bloom of Akkermansia muciniphila in association with changes in gut gene expression consistent with attenuated metabolic syndrome symptoms. Here we investigated the timing of GP-induced effects and identified the main class of GP responsible for the A. muciniphila bloom. In two 14-day time course studies mice were fed high- or low-fat diets (HFD, LFD) or isocaloric ingredient-matched formulations supplemented with 1% grape polyphenols (HFD-GP, LFD-GP). Mice fed HFD-GP for two weeks showed significantly improved oral glucose tolerance (OGT) compared to control, while LFD and LFD-GP groups displayed similar OGT. A. muciniphila bloom was detected earlier in mice fed LFD-GP than HFD-GP; however, difference in timing of this GP-induced bloom was more dependent on baseline abundance of A. muciniphila in the two cohorts of mice than on dietary fat. Indeed, only mice with qPCR-detectable levels of A. muciniphila developed a GP-induced bloom within 3 days. The GP-induced bloom in A. muciniphila occurred before specific intestinal gene expression changes associated with metabolic resilience. Finally, compared to vehicle, mice dosed for 10 days with GP extract (GPE) or an equivalent dose of purified oligomeric grape proanthocyanidins (PAC) showed similar increases in fecal and cecal A. muciniphila. These data suggest that PAC-induced modification of the gut microbiota precedes changes in host gene expression and phenotypes associated with metabolic health.

The Microbial Metabolome: The Missing Link Between Diet and Human Health

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The gut microbiota plays a role in the development of disorders such as T2DM, CVD and cancer. Despite tremendous advances characterizing microbial diversity, little is known about the functional role of even the most dominant species. It is widely accepted that microbial metabolites are likely to impact on human health, particularly regarding immune response and inflammation, but these are not characterised and their mechanism of action unknown. Dietary substrates (cereals/soft fruit/green leafy vegetables/soya) considered to contribute towards cancer prevention were characterized for their nutrient and phytochemical composition before and after in vitro digestion. Using sequenced microbial samples from volunteers taking part in the human intervention with these foods, the products of microbial metabolism were determined. Explicit transformations of the major phytochemicals were observed by fully targeted metabolomics, but inter-individual variation demonstrated key activities that highlighted the importance of certain species to shape the microbial metabolome. In particular, polyamine metabolism differed and similar differences were observed for aromatic amino acid and phytoestrogen transformations. Notable was phenolic metabolism, as the profiles produced are likely to impact on inflammation. Using an extensive library of model compounds and cultured bacteria, the mechanism and species responsible for many of these transformations were identified and are currently

being validated in human studies to ensure that the same results are observed in vivo. This data will help elucidate the complex interplay between diet, the gut microbiota and the role by which they contribute to maintenance of health and disease development.

Characterization of Fecal Microbiota in Response to Heterologous Versus Autologous Fecal Microbial Transplantation

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Fecal microbial transplantation (FMT) has been increasingly used as an alternative treatment for recurrent Clostridium difficile infections (RDCI), with a success rate averaging 90%. The fecal microbial compositions of heterologous and autologous FMT recipients were characterized using Illumina next-generation sequencing of the V5+V6 hypervariable regions of the 16S rRNA gene, 5 days prior to FMT, and at 2 and 8 weeks post-FMT. Bacterial communities prior to FMT were dysbiotic and characterized at the phylum level by drastic reduction or disappearance of Bacteroidetes and expansion of the Proteobacteria and/or Verrucomicrobia. Abundances of Verrucomicrobia and Bacteroidetes in pre-FMT samples were notably greater at the Bronx site, where greater autologous FMT success was observed. Heterologous FMT restored the bacterial community alpha diversity to resemble that of healthy donors, while the bacterial community composition in fecal samples of patients also shifted to one similar to donor samples. Community composition after autologous FMT was significantly different than that resulting from heterologous FMT at both sites ($P \leq 0.025$), and the abundance of Bacteroidetes did not recover to the same extent as was observed in patients who received heterologous donor material. These data reveal that autologous FMT results in different community composition than heterologous FMT, with the latter providing faster and more marked resolution of dysbiotic microbial signatures.

Dynamic Longitudinal Transcriptome Differences Across Healthy and Respiratory Viral Infections and Between Pre-Diabetic and Non-Diabetic States

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To better understand how longitudinal omics information can be incorporated into health care and how physiology changes during periods of healthy and respiratory viral infections (RVI), we are performing a large scale integrated Personal Omics Profiling (iPOP) combining genomic and transcriptomic data in a cohort of 100 individuals (over 1000 time points in total) who experienced several RVI and immunization (flu shots) and are either insulin resistant (IR) or insulin sensitive (IS). Our data shows that there is a strong defense response upon RVI and activation of different immunological pathways over the course of infection and recovery times. It initially activates type I interferon signaling pathway, pattern recognition receptors and Toll-like receptors within 1-3 days upon RVI, while after seven days, granzymes and T-helper cells, and within 21 to 35 days Interleukins (IL6, IL10, IL17A, IL17F), MAPK3 and JAK2 in cytokine signaling get activated. However, immunizations, on the contrary, did not activate the immune system, but differentially expressed genes were enriched for GABA, Leptin, and GPCR signaling pathways. Moreover, the number of differentially expressed genes related to immune system upon RVI

is significantly higher among insulin sensitive (IS) individuals compared to the insulin resistant (IR) ones that could potentially suggest a stronger immune defense response in IS individuals. Also, 25% of participants show a temporary dys-regulation in genes involved in neurodegenerative diseases upon RVI. Altogether, these results shed light on how immune system responses to RVI over time and how this response differs between IS and IR individuals.

Early Microbial Antigen Priming Sets the Course for Host Immune Tolerance vs. Immunity

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Life in a microbial world requires adaptive immune tolerance to commensal microbes and effective immune responses to infectious pathogens. However, mechanisms allowing the host to establish a privileged relationship with commensals while still defending against pathogens remain largely unknown. Using tetramers for a model bacterial antigen, 2w, we can track the antigen-specific CD4+ T cell response to S. epidermidis (SE-2W), a prominent skin commensal, and S. aureus USA300 (SA-2W), a prototypical skin pathogen. As previously shown, SE-2W skin colonization in neonatal life establishes 2W-specific immune tolerance, which is mediated by regulatory T cells (Tregs) entering neonatal skin. In contrast, we find that neonatal SA-2W colonization does not protect against skin inflammation nor significantly enrich for 2W-specific Tregs upon subsequent SA-2W challenge. Following initial bacterial exposure, SA-colonized neonates had equivalent or higher total numbers of skin Tregs compared with SE-colonized counterparts, indicating that failure to establish tolerance to SA-2W was not due to attenuated skin Treg accumulation. SE-2W but not SA-2W colonization, however, enriched for 2W+Tregs following intradermal 2W peptide challenge, consistent with a model in which differential T cell priming upon initial microbial antigen exposure sets the course for tolerance or immunity. RNA sequencing of Tregs and FoxP3negCD4+ T cells from the skin of SE vs. SA-colonized neonates has revealed key upstream regulators that may direct this differential T cell response. Ongoing work to be presented will measure the contribution of these key host pathways as well as bacterial molecules in the host's "decision" for microbial tolerance vs. immunity.

Temporal Dynamics of Metatranscription in Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is a group of chronic diseases of the digestive tract with no effective long-term treatment options. One of the major breakthroughs in recent years was the elucidation of the human microbiome's role in onset and exacerbation of IBD. In particular, the mechanisms associating gut microbial dysbioses and aberrant immune responses remain largely unknown. The integrative Human Microbiome Project (iHMP/HMP2) seeks to close these gaps by examining the dynamics of microbiome functionality in disease. As part of this effort, the IBD Multi'omics Database (IBDMDB) profiled the gut microbiomes of 100 individuals using multiple high-throughput, functional genomic screens over the course of one year each. Here, we present the results based on the pilot data including

300 stool metagenomes and 78 metatranscriptomes, spanning 117 individuals with up to 17 time points. While some microbial organisms exhibited similar expression patterns on DNA and RNA level, we also detected species-specific biases in metabolic activity. For example, while Faecalibacterium prausnitzii was in many cases not the most prevalent organisms in a sample, it was for many pathways the major transcriber. Further, certain disease characteristics were particularly detectable at the transcript level, such as pathways metagenomically uniform between IBD patients compared to non-IBD controls but metatranscriptomically contributed by distinct organisms (e.g. Alistipes putredinis). These IBDMDB pilot studies thus pave the way for analysis of the iHMP data incorporating metabolomics, host transcriptomics, epigenetics, and genetics as well as provide new opportunities for the discovery of novel diagnostic and therapeutic approaches in IBD.

Unraveling the Microbiome of Primary Immune-Deficient Patients

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Although landmark studies have shown that microbiota activate and educates host immunity, how the immune system shapes microbial communities and contributes to disease is less-well characterized. Studying primary immunodeficiency patients provides a unique perspective on the degree to which altered immunity may influence the human microbiome and how, in turn, microbiota may interact with the host to develop disease. DOCK8 (dedicator of cytokinesis 8) deficiency is an extremely rare autosomal recessive primary immunodeficiency disease manifesting with persistent viral infections of the skin, atopic dermatitis, allergies and skin and hematopoietic malignancies.

To study the human virome, we applied shotgun metagenomics to multiple skin, oral and stool samples from 20 DOCK8 patients. While the relative abundance of eukaryotic viruses on the skin of healthy volunteers is 0.1-10%, DOCK8 patients typically have >90% eukaryotic viruses forming the skin microbial community. Our analyses revealed that the skin DNA virus communities in these patients are dominated by multiple types of human papillomaviruses (HPVs), including hundreds of alpha, beta, gamma and mu HPVs. Using computational tools, such as de-novo assembly, we could also identify numerous possible novel HPVs that share less than 90% nucleotide sequence identity with the conserved L1 capsid protein of any other known HPV. With RNA-Seq, we identify even greater viral diversity, indicating a much greater potential of eukaryotic viruses to colonize the human body.

Multi-Omic Microbiome Study-Pregnancy Initiative (MOMS-PI)

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The vaginal microbiome in pregnancy plays an important role in both maternal and neonatal health outcomes. Despite the critical role of the human microbiota in health, our understanding of microbiota compositional dynamics during pregnancy is incomplete. The Vaginal Microbiome Consortium at VCU and its collaborators, including the GAPPS based at Seattle Children's Hospital, has collected longitudinal samples from pregnant women in the MOMS-PI study. Samples were collected during prenatal visits at

all trimesters (3-7 visits), Labor and Delivery, discharge and follow-up visit from >1,500 pregnant women and their neonates. We currently have >150,000 samples (buccal, vaginal, cervical, skin, blood, urine, cord, cord blood, placenta and membranes) from MOMS-PI in our RAMS registry biorepository. The cohort is ~50% African American, ~45% Caucasian, and ~25% Latina/Hispanic (split between African American and Caucasian). To date, we have analyzed >10,000 of these samples for microbiome profiling by 16S rRNA, and several thousand for cytokine, lipidome, metagenomics and metatranscriptomic analysis. Our results confirm a uniquely complex microbiome in the female reproductive tract that shows racial biases, is altered during pregnancy, and is impacted by environmental and clinical factors. Multi-omic analysis of our preliminary data shows correlations between taxonomic, cytokine, and lipidome profiles, and clinical observations. These results are altering the traditional view of women's vaginal and reproductive health, leading to a functional understanding of the mechanisms leading to adverse health and pregnancy outcomes, permitting earlier prediction and potentially earlier intervention to prevent adverse reproductive events.

A Protective Major Histocompatibility Complex-Class II Allele Prevents Autoimmune Diabetes by Shaping the Intestinal Microbiome Early in Ontogeny

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Certain major histocompatibility complex-class II (MHC-II) or human leukocyte antigen-D (HLA-D) alleles dominantly protect from particular autoimmune diseases. For example, expression of the MHC-II E:E complex potently protects NOD mice, which normally lack it, from spontaneous development of type-1 diabetes (T1D). However, the underlying mechanisms remain debated. We investigated MHC-mediated protection from T1D using previously reported NOD mice expressing an E transgene and, thereby, the E:E complex. E16/NOD females vertically protected their NOD offspring from diabetes and insulitis, in an intestinal-microbiota-dependent fashion, and developed autoimmunity when treated with particular antibiotics or raised in a germ-free environment. Genomic analysis revealed NOD and E16/NOD mice to host distinct intestinal microbiotas during a critical early window of ontogeny, and transfer of cecal contents from the latter to the former suppressed insulitis. Thus, this protection from autoimmunity afforded by particular MHC/HLA alleles can operate via intestinal microbes, highlighting potentially important societal implications of treating infants, or even just their pregnant mothers, with antibiotics. These findings argue for a new model of HLA/MHC-mediated protection from autoimmunity, and raise the question of whether disease-protective alleles in other human autoimmune diseases or models thereof, e.g., rheumatoid arthritis or multiple sclerosis, might operate by a similar mechanism.

The Impact of Sex, Age, and Diet on the Microbiome and Metabolome

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It is well known that diet profoundly affects the microbiome and metabolome. In particular, a western style diet high in fat and sugar has been associated with development of obesity, metabolic syndrome, and NAFLD. While approximately equal numbers of men and women are obese, it has been reported that NAFLD is more prevalent in males. In this study, we provided either a western or control diet to C57BL/6J mice starting at 3 weeks, sacrificed mice at 5, 10, and 15 months of age, and compared the

urine and serum metabolomes, as well as fecal and cecal microbiomes. PCA of the urine metabolome revealed complete separation along PC2 based on sex, with some separation along PC1 based on diet. For the serum metabolome, age drove separation along PC2, with some separation along PC1 based on diet. Sex-based metabolome distinctions pointed to differences in several pathways regulated by estrogen, as well as TMA/TMAO. Diet-based metabolome distinctions pointed to differences in metabolites related to insulin sensitivity and production of TMA/TMAO, and age-based metabolome distinctions pointed primarily to differences in ketone production. Interestingly, 16S rRNA marker gene sequencing of fecal and cecal contents revealed similar results to the urine metabolome, with sex and diet driving separation. Remarkably, we observed a major shift in the microbiome of female mice at 15 months compared to 5 and 10 months, suggesting that estrogen may play a role in shaping the microbiome. Taken together, our results suggest that sex and age differences in the microbiome and metabolome may correlate with a protective effect of estrogen on health.

Regulation of Host-Microbiota Relationships in Human Health and Disease

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The human immune system is critical to protect against infection with pathogenic microorganisms. However, inappropriate immune responses against our own tissues or non-harmful environmental triggers such as beneficial commensal bacteria that normally colonize the body's barrier surfaces can promote autoimmune or chronic inflammatory diseases. Indeed, emerging studies in patient populations indicate that abnormal host immune responses to commensal bacteria are causally linked to the pathogenesis and progression of numerous chronic infectious, inflammatory and metabolic diseases, such as HIV, inflammatory bowel disease (IBD) and cancer. The focus and long-term research goals of the Sonnenberg Laboratory are to interrogate functional interactions between the mammalian immune system and intestinal commensal bacteria in the context of health and disease. The laboratory employs cutting-edge immunologic and microbiologic approaches to interrogate these interactions in both basic mouse models and translational patient-based studies. Recent studies in the laboratory have identified a critical role for innate lymphoid cells in orchestrating host relationships to defined subsets of commensal bacteria. Delineating these complex interactions will lead to a better understanding of the pathogenesis of multiple chronic inflammatory diseases, and direct the future development of novel therapeutic strategies targeting commensal bacteria-dependent chronic inflammation.

Akkermansia Muciniphila May Be Permissive to Arthritis in the K/BxN Mouse Model of Arthritis

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Background: Studies have identified abnormalities in the microbiota of patients with arthritis. To evaluate the pathogenicity of human microbiota, we performed fecal microbial transplantation (FMT) from children with newly diagnosed enthesitis-related arthritis (ERA) and sex- and age-matched healthy

controls (HC) to germ-free KRN/B6xNOD (K/BxN) mice, a spontaneous arthritis model dependent upon an intact microbiota. **Methods:** K/BxN mice were maintained under germ-free (GF) conditions and were gavaged with feces previously collected from children with ERA and HC. **Results:** 24 mice were gavaged with human microbiota (12 each of ERA and HC). Among transplanted mice, ankle swelling assessed 21 – 24 days post transfer was equivalent in those that received ERA (4.7 ± 0.5) vs HC (4.4 ± 0.4) microbiota. There was incomplete uptake of the human microbiota, with over-representation of two genera (Bacteroides and Akkermansia) in the transplanted mice. The microbiota as a whole predicted the extent of ankle swelling (R2 = 0.185, p = 0.018, adonis test); the abundances of Bacteroides (r = -0.510, p = 0.010) inversely and Akkermansia (r = 0.367, p = 0.078) directly correlated with ankle swelling. Although monocolonization of A. muciniphila did not impact ankle swelling, addition of A. muciniphila cultures to transplanted human microbiota resulted in increased ankle swelling as compared to mice that received transplanted human microbiota alone (median 4.5 mm, IQR 4.3 – 5.5 versus 4.1 mm, IQR 3.9 – 4.3, p = 0.018). **Conclusions:** This study supports previous findings of a possible association between A. muciniphila and arthritis and opens up new avenues of research into the association between human microbiota and arthritis.

A Disease-Protective Human Commensal Discovered Using Microbial Pedigree Analysis

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Microbiome-wide association studies have established that numerous diseases are associated with changes in the microbiota. These studies typically generate a long list of commensals implicated as biomarkers of disease, with no clear relevance to disease pathogenesis. In order to move the field beyond correlations and to begin to address causation, an effective system is needed for refining this catalog of differentially abundant microbes for subsequent mechanistic studies. Herein, we demonstrate that principles of family pedigree analysis used in genetics can be applied in microbiota studies to reduce the noise inherent in these experiments. We found that gnotobiotic mice harboring different microbial communities exhibited differential survival in a colitis model. Co-housing of these gnotobiotic mice generated "progeny" that had hybrid microbiotas reflective of both "parents" and displayed intermediate susceptibility to colitis. Mapping of microbe-phenotype relationships in parental mouse strains and in mice with hybrid microbiotas identified the bacterial family Lachnospiraceae as a correlate for protection from disease. Using directed microbial culture techniques, we discovered Clostridium immunis, a previously unknown bacterial species from this family, that—when administered to colitis-prone mice—protected against colitis-associated death. Thus, we have used "microbial pedigree" analysis to move beyond the standard correlative microbiome study and found a hitherto unidentified commensal that causally protects from colitis. More broadly, identifying disease-modulating commensals by means of microbial pedigree analysis may also be applicable to human microbiome studies.

The Interplay Between Gut Microbiota-Derived Secondary Bile Acids and C. Difficile Pathogen Dynamics

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The changing epidemiology of Clostridium difficile infection over the past decades presents a significant challenge in the management of C. difficile associated diseases. The gastrointestinal tract microbiota provides colonization resistance against C. difficile, and growing evidence suggests that gut microbial derived secondary bile acids (SBAs) play a role. We hypothesized that the C. difficile life cycle; spore germination and outgrowth, growth, and toxin production, of strains that vary by age and ribotype will differ in their sensitivity to SBAs. C. difficile strains R20291 and CD196 (ribotype 027), M68 and CF5 (017), 630 (012), BI9 (001) and M120 (078) were used to define taurocholate (TCA) mediated spore germination and outgrowth, growth, and toxin activity in the absence and presence of gut microbial derived SBAs (deoxycholate, isodeoxycholate, lithocholate, isolithocholate, ursodeoxycholate, ω-muricholate, and hyodeoxycholate) found in the human and mouse large intestine. C. difficile strains varied in their rates of germination, growth kinetics, and toxin activity without the addition of SBAs. C. difficile M120, a highly divergent strain, had robust germination, growth, but significantly lower toxin activity compared to other strains. Many SBAs were able to inhibit TCA mediated spore germination and outgrowth, growth, and toxin activity in a dose dependent manner, but the level of inhibition and resistance varied across all strains and ribotypes. This study illustrates how clinically relevant C. difficile strains can have different responses when exposed to SBAs present in the gastrointestinal tract.

Strain-Level Identification of Mother-to-Child Bacterial Transmission During the First Few Months of Life

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The human gut microbiota is established during the first few years of life, yet we know remarkably little about the natural history of how the microbiome forms in children. Early events in microbial colonization have a profound effect on physiology and immune education in the gut, thereby impacting disease susceptibility (e.g., obesity, asthma, and other inflammatory disorders later in life).

Using a newly established prospective birth cohort, we studied the gut microbiome of 24 infants and their mothers, sampled longitudinally in the first few months of the child's life. We compared the microbial communities across and within families to identify bacterial transmission events.

We found that newborn samples collected within two days of delivery exhibit low-complexity microbial communities, where often 1-4 species account for >85% of the community. Using species-level abundance profiles, we can identify communities dominated by either E. coli, Bifidobacterium, or

Staphylococcus species. We next used deep metagenomic sequencing to identify strains by comparing SNPs across the genomes of these highly abundant species. Despite the species-level similarity across unrelated children, strain-level analysis reveals unique shared strains that are transferred from mothers to their children.

The Human Gut Microbiome Protects Against Arsenic Toxicity

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Arsenic is a toxin and carcinogenic metalloid that poisons an estimated 200 million people around the world, primarily through contaminated food and drinking water. In humans and other mammals, the relative influence of different cell types capable of arsenic detoxification has been debated. Confusingly, the mammalian microbiome has been suggested to both mitigate and exacerbate arsenic toxicity. Here we show that the human gut microbiome protects from arsenic-induced mortality in vivo. We found that both antibiotic-treated and germ free mice excreted significantly less arsenic in stool and accumulated more arsenic in organs compared to untreated, conventional mice. We also found that mice lacking the primary arsenic detoxification pathway (arsenic 3+ methyltransferase, As3mt) were hypersensitive to arsenic after antibiotic treatment or when derived germ free compared to wild-type and/or conventional counterparts. We then found that human microbiome (stool) transplants protected As3mt-KO mice from arsenic-induced mortality, but that the level of protection correlated with microbiome stability and presence of the well-known human commensal, Faecalibacterium. Our results demonstrate that both a functional As3mt and a stable microbiome are required for protection against arsenic toxicity. We anticipate that the gut microbiome will become an important explanatory factor of disease (arsenicosis) penetrance in human populations, and a novel target for prevention and treatment strategies.

The Importance of Colonization History in Gut Microbiota Assembly

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The ecological processes that govern assembly of the gut microbiota and contribute to the vast compositional variation among individuals are still insufficiently understood. Deterministic factors explain neither the entire magnitude of inter-individual variability nor the full range of characteristics of the microbiota across individuals. Here, we employed gnotobiotic mice to systematically examine the importance of colonization history in shaping the gut microbiota. Germ-free wild-type (WT) and Rag1-/- C57BL/6 mice were inoculated at two time points (weeks 1 and 6) with distinct mouse cecal microbiomes (A & B) in different succession (A/B or B/A) or together (AB/AB), and the microbiota was characterized at week 12. In additional experiments, four bacterial stains were introduced into mice at different time points to test how time of acquisition influences colonization success and the trajectory of community assembly. Measures of beta-diversity revealed that the assembled microbiota was statistically more similar to the donor community established first, indicating an importance of colonization order. In addition, persistence was enhanced for two of the four bacterial strains tested when introduced during the first week of life compared to later time points. The advantage of early

colonization appears to result from ecological processes with little involvement of the adaptive immune system, as analogous results were observed in WT and Rag1-/- mice. In conclusion, this study established the importance of colonization history for gut microbiota assembly, providing basic information to both understand inter-individual variation of the gut microbiome and develop strategies to counteract aberrant patterns of colonization.

Microbe-Mitochondria Interaction in Host Longevity Regulation

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Microbes residing in the host gut actively produce various metabolic molecules that exert crucial effects on host health. However, the exact molecular relationship between microbe-derived metabolites and host longevity remains largely unknown. Through high-throughput genetic screens, we have identified specific microbes and their-derived metabolites that specifically regulate host longevity in Caenorhabditis elegans. We further delineated molecular pathways regulated by these microbial metabolites in the host, and discovered host mitochondrial dynamics as a converged cellular mechanism for these longevity regulations. Together, our work reveals microbe-host metabolic axes that control mitochondrial dynamics with critical consequences for host metabolic health and longevity.

Vibrio Cholerae Infection and the Duodenal Microbiome

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Introduction: Studies of household contacts exposed to Vibrio cholerae have identified gut microbial factors that are associated with susceptibility to infection. To detect microbial species that may interact with V. cholerae during human infection, we prospectively examined the gut bacteria adherent to the duodenal mucosa, a site of V. cholerae replication in humans. **Methods:** We examined the duodenal and stool microbiome of 17 Bangladeshi patients with active cholera using 16S rRNA sequencing. Duodenal pinch biopsies (collected by esophagogastroduodenoscopy) and stool were collected on day 2 following onset of infection, and at two follow up timepoints. **Results:** During cholera, fewer bacteria were present in the duodenal mucosa compared to follow up timepoints (average of 2473 reads per sample, compared to 4749 reads per sample on follow up days, p=0.01, unpaired t test). Bacterial populations during cholera were phylogenetically distinct compared to follow up timepoints (p=0.002, unweighted Unifrac distances permutational multivariate analysis of variance). During cholera, the duodenal microbiota was also characterized by a decrease in anaerobes (such as phylum Proteobacteria, p=0.02, unpaired t test), and increases in specific Gram-negative genera, such as Halomonas and Shewanella (8% versus 3% at baseline, and 3% versus 0.1 % at baseline, respectively, linear discriminant analysis score >4.0). The duodenal and stool microbiome recovered to baseline by day 30. **Conclusion:** We studied mucosal bacteria from the active site of V. cholerae infection to identify species that may influence clinical outcomes. The biological interactions between the dominant bacterial groups during active V. cholerae warrant further study.

Antibiotic-Induced Microbiome Depletion Alters Glucose Homeostasis by Affecting Intestinal Signaling and Colonic Energy Metabolism

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Antibiotic-induced microbiome depletion (AIMD) can reveal the relationship of the gut microbiome and host glucose homeostasis by affecting luminal secondary metabolites and gut signaling. We investigated the effects of AIMD in normal-chow fed mice to understand its effects on gut homeostasis, luminal signaling, and metabolism. We show that AIMD decreases baseline serum glucose levels, reduces glucose surge in a tolerance test, and improves insulin sensitivity without altering food intake or body adiposity. These occur in the setting of decreased luminal SCFAs, especially butyrate, and secondary bile acid (BA) pool which affects whole-body BA metabolism. AIMD mice have altered cecal gene expression and gut signaling, particularly of GLP-1. Extensive tissue remodeling and decreased availability of SCFAs shift enterocyte metabolism toward glucose utilization. Hence, AIMD alters whole-body glucose homeostasis by potentially converting the gut into a glucose sink.

Antibiotics Disrupt Gastrointestinal Microbiota and Mucosal Immunity in Rhesus Macaques

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Antibiotics are widely used throughout the world to treat bacterial infections. However, mounting evidence suggests that antibiotic therapies can disrupt the composition of the gastrointestinal (GI) microbiome. GI-resident microbiota and their metabolites, such as short chain fatty acids (SCFAs) are critical for maintaining host immune homeostasis and protecting against the expansion of pathobionts. We administered antibiotics to four groups of healthy female rhesus macaques and collected GI biopsies and with stool. We evaluated mucosal immunity before, during, and after the antibiotic treatments and tracked bacterial community composition using 16S rRNA gene sequencing. Finally, we used GC-MS to evaluate stool concentrations of SCFAs. The antibiotic treatments were linked to shifts in bacterial communities in the stool, as well as dramatically decreased concentrations of all measured SCFAs. We demonstrated changes in mucosal immunity during the antibiotic treatment, including a significant increase in colonic and rectal mucosal neutrophils during the treatment, and altered frequencies of colonic activated CD4+ T-cells, and IL-17 producing CD4+ T-cells. Thus, antibiotic therapies can alter GI bacterial abundance, lead to a decrease in SCFAs, and are linked to a distinct signature of mucosal inflammation. These data demonstrate how altering the structure and function of GI bacterial communities can have a profound effect on mucosal immunity.

Integrative Personal Omics Profiles During Periods of Weight Gain and Loss

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Obesity is a worldwide health epidemic and a major cause for cardiovascular disease and acquired insulin resistance leading to type 2 diabetes mellitus (T2DM). The detrimental health effects of short-term excess weight gain are poorly understood. Here we performed a longitudinal study combining multiple omics strategies (genomics, transcriptomics, proteomics, metabolomics and microbiomics) to comprehensively characterize biomolecular changes in the blood and microbiomes of healthy and insulin resistant human subjects during periods of experimental weight gain and loss. Longitudinal multi-omic profiling revealed a wealth of biomolecular changes concomitant with weight gain, including pathways associated with glucose regulation/metabolism, and the activation of strong inflammatory and hypertrophic cardiomyopathy signatures in the blood. In total, these large-scale longitudinal data offer a novel view of the rapidly-changing biomolecular landscape associated with weight gain/loss and may offer new strategies for predicting and preventing obesity-associated metabolic and/or cardiovascular disease. The data also serve as a unique resource for the scientific community.

Effects of Intermittent Fasting on the Gut Microbiome in Multiple Sclerosis

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Background: Calorie restriction (CR) ameliorates experimental autoimmune encephalomyelitis (EAE), the animal model of MS. However, the exact mechanism by which CR affects the EAE course is unknown. The gut microbiome is strongly influenced by diet. Gut microbiome also plays an important role in regulating host immunity. Here, we aim to test the effects of intermittent fasting (IF) on clinical course, immune responses and gut microbiome in EAE and MS patients. **Methods:** C57BL/6 mice were kept on a regimen of IF or ad libitum (controls) for a month prior to immunization with MOG35-55 and during EAE. Immune profiling in peripheral and gut associated lymphoid organs and stool microbiome were analyzed. Fecal transplant from IF to control group was performed. RRMS patients were randomized to IF group and control group. Stool and blood samples were analyzed before and after 15 days of IF. **Results:** The IF group displayed a less severe EAE clinical course. Production of IL17 by T cells in the draining lymph nodes of the site of immunization was attenuated in IF mice. IF increased the number of regulatory T cells in mesenteric lymph nodes. IF significantly altered the diversity and the composition of gut microbiome. Fecal transplant of the IF-altered gut microbiome ameliorated EAE severity. Microbiome in MS patients on IF indicated similar changes as mice undergoing IF. **Conclusions:** IF can ameliorate EAE clinical course by modulating immune response, affecting the composition of immune cells in gut associated lymphoid tissue and drastically changing the gut microbiome.

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