

# PRECISION PROBIOTIC

# THERAPIES

### Challenges and Opportunities

April 26–27, 2022

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### AGENDA

#### Tuesday, April 26, 2022

### What Are the Current Challenges in Probiotic Research?

10:00 – 10:05 a.m.	Welcome Barbara C. Sorkin, Ph.D., M.S., Office of Dietary Supplements (ODS) Hye-Sook Kim, Ph.D., National Center for Complementary and Integrative Health (NCCIH)
10:05 – 10:10 a.m.	Opening Remarks Helene M. Langevin, M.D., Director, NCCIH
10:10 – 10:50 a.m.	Keynote Speaker Jeffrey Gordon, M.D., Washington University in St. Louis. Microbiome-directed complementary foods for treating childhood undernutrition
10:50 a.m.	Session One: Current Challenges in Clinical Trials
10:50 – 10:55 a.m.	Moderators: Gabriela Riscuta, M.D., M.S., C.N.S., National Cancer Institute (NCI) R. Dwayne Lunsford, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
	Speakers:
10:55 a.m.	<b>Rima Kaddurah-Daouk, Ph.D.,</b> Duke University. <i>Metabolome,</i> <i>genome, diet, and exposome: toward a precision medicine approach</i> <i>for probiotic therapies</i>
11:10 a.m.	Daniel Merenstein, M.D., Georgetown University. Challenges in precision probiotic clinical trials: is it even possible?
11:25 a.m.	Mark Haupt, M.D., International Flavors & Fragrances. An introduction to the importance of investigational product manufacturing for probiotic intervention trials
11:40 – 11:45 a.m.	Break
11:45 a.m.	<b>Susan Lynch, Ph.D.,</b> University of California, San Francisco. <i>Probiotic clinical trials—an opportunity to move toward precision</i> <i>microbiome manipulation</i>
12:00 p.m.	Sarkis Mazmanian, Ph.D., California Institute of Technology. Gut microbial metabolites in human and animal behavior

12:15 p.m.	Rajita Menon, Ph.D., Vedanta Biosciences. Opportunities and challenges in development of medicines based on defined bacterial consortia
12:30 – 1:30 p.m.	Panel Discussion
1:30 – 2:00 p.m.	Lunch Break
2:00 p.m.	Session Two: Host-Microbiome Interactions in Precision Probiotic Research
2:00 – 2:05 p.m.	Moderators:
	Ashley Vargas, Ph.D., M.P.H., R.D.N., Eunice Kennedy Shriver National Institute of Child Health and Human Development
	Frank A. Hamilton, M.D., M.P.H., M.A.C.G., A.G.A.F., NIDDK
	Speakers:
2:05 p.m.	Justin Sonnenburg, Ph.D., Stanford University. Controlled engraftment and abundance of next-generation probiotic therapies
2:20 p.m.	Purna C. Kashyap, M.B.B.S., Mayo Clinic. Multiomics to mechanisms: the road to microbiome-driven precision medicine
2:35 p.m.	<b>Gianna Hammer, Ph.D.,</b> Duke University. <i>Keeping it "old school"—</i> the influence of the microbiome on responses, regulation, and metabolic rewiring of long-lived, fetal-derived immune cells
2:50 p.m.	Jun Huh, Ph.D., Harvard University. Microbial metabolites of bile acids in controlling host immune cell function
3:05 p.m.	Amir Zarrinpar, M.D., Ph.D., University of California, San Diego. The microbiome and time: using engineered bacteria to understand microbiome-circadian relationships
3:20 – 3:30 p.m.	Break
3:30 p.m.	<b>Sharon M. Donovan, Ph.D., R.D.,</b> University of Illinois, Urbana-Champaign. <i>Noninvasive interrogation of host-microbiome</i> <i>crosstalk in the human infant</i>
3:45 p.m.	Steven D. Townsend, Ph.D., Vanderbilt University. Application of 2'-fucosyl lactose in preventing intestinal injury
4:00 p.m.	Liping Zhao, Ph.D., Rutgers University. Reference-free and guild- based approach for discovering novel probiotic bacteria with ecological competency
4:15 p.m.	Andrew Goodman, Ph.D., Yale University. <i>Microbiome contributions</i> to drug metabolism
4:30 – 5:30 p.m.	Panel Discussion
5:30 – 5:35 p.m.	Closing Remarks and Adjourn
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### Wednesday, April 27, 2022

### What Will Be the Next Steps in Precision Probiotics?

10:00 – 10:05 a.m.	Welcome Barbara C. Sorkin, Ph.D., M.S., ODS Hye-Sook Kim, Ph.D., NCCIH
10:05 – 10:10 a.m.	Opening Remarks Joseph M. Betz, Ph.D., Acting Director, ODS
10:10 – 10:50 a.m.	Keynote Speaker Gary Wu, M.D., University of Pennsylvania. The gut microbiome in IBD as a prototype for the opportunities and challenges in the development of precision probiotics: the next steps
10:50 a.m.	Session Three: Next Generation Probiotics – New Strain Identification and Development
10:50 – 10:55 a.m.	Moderators: Padma Maruvada, Ph.D., NIDDK Ryan Ranallo, Ph.D., National Institute of Allergy and Infectious Diseases
	Speakers:
10:55 a.m.	Julia Oh, Ph.D., The Jackson Laboratory. From metagenomes to therapeutics: the human skin microbiome
11:10 a.m.	June L. Round, Ph.D., University of Utah. Microbiota-immune interactions that promote intestinal health
11:25 a.m.	Jan Peter van Pijkeren, Ph.D., University of Wisconsin–Madison. Bioengineered probiotics to deliver therapeutics
11:40 – 11:45 a.m.	Break
11:45 a.m.	Tami Lieberman, Ph.D., Massachusetts Institute of Technology. Inferring in-human commensal biology by reconstructing within- person bacterial evolution
12:00 p.m.	Erwin G. Zoetendal, Ph.D., Wageningen University & Research. Novel probiotics from our microbiome
12:15 p.m.	<b>Rustem F. Ismagilov, Ph.D.,</b> California Institute of Technology. Small intestine and microbes are central to human health, but understanding their role requires quantitative tools applied to human (not animal) samples
12:30 – 1:30 p.m.	Panel Discussion

1:30 – 2:00 p.m.	Lunch Break
2:00 p.m. 2:00 – 2:05 p.m.	Session Four: Emerging Technologies for Precision Probiotics Moderators: Mukesh Verma, Ph.D., NCI Terez Shea-Donohue, Ph.D., NIDDK
	Speakers:
2:05 p.m.	<b>Hyun Jung Kim, Ph.D.,</b> University of Texas at Austin. A pathomimetic intestinal disease-on-a-chip for validating microbiome-based therapeutics
2:20 p.m.	<b>Tom Van de Wiele, Ph.D.,</b> Ghent University. <i>Personalization of human gut models to bridge knowledge gaps regarding interindividual variability in efficacy and mode of action of precision probiotics</i>
2:35 p.m.	Noah Palm, Ph.D., Yale University. Mapping uncharted landscapes of host-microbiota connectivity
2:50 p.m.	Emily P. Balskus, Ph.D., Harvard University. Deciphering the human microbiome with chemistry
3:05 p.m.	Curtis Huttenhower, Ph.D., Harvard University. Probiotic bioactivity in the human microbiome
3:20 p.m.	Barbara Rehermann, M.D., NIDDK. Wild mouse microbiota and pathogens in preclinical research models
3:35 p.m.	Sameer Sonkusale, Ph.D., Tufts University. Lab-on-a-pill for spatially targeted sampling of gut microbiome
3:50 – 4:00 p.m.	Break
4:00 – 5:00 p.m.	Panel Discussion
5:00 – 5:10 p.m.	Closing Remarks and Adjourn

### OPENING REMARKS



#### Helene M. Langevin, M.D., National Center for Complementary and Integrative Health

Dr. Langevin is the director of the National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH). As NCCIH director, she oversees the Federal government's lead agency for research on the fundamental science, usefulness, and safety of complementary and integrative health approaches and their roles in improving health and health care. Prior to coming to NIH, Dr. Langevin served as director of the Osher Center for Integrative Medicine, jointly based at Brigham and Women's Hospital and Harvard Medical School, Boston. She also previously served as professor of neurological

sciences at the University of Vermont Larner College of Medicine, Burlington, Vermont. Dr. Langevin's research interests have centered around the role of connective tissue in chronic musculoskeletal pain and the mechanisms of acupuncture and manual and movement-based therapies. Her recent work has focused on the effects of stretching on inflammation resolution mechanisms within connective tissue. She has authored more than 70 original scientific papers and is a fellow of the American College of Physicians. Dr. Langevin received an M.D. degree from McGill University, Montreal. She completed a postdoctoral research fellowship in neurochemistry at the MRC Neurochemical Pharmacology Unit in Cambridge, England, and a residency in internal medicine and fellowship in endocrinology and metabolism at The Johns Hopkins Hospital in Baltimore, Maryland.

### **KEYNOTE SPEAKER**



#### Jeffrey Gordon, M.D., Washington University in St. Louis

Dr. Gordon is the Dr. Robert J. Glaser Distinguished University Professor at Washington University in St. Louis. He received his M.D. from the University of Chicago. After completing his clinical training in internal medicine and gastroenterology and doing a postdoctoral fellowship at the National Institutes of Health, he joined the faculty at Washington University, where he has spent his entire career—first as a member of the Departments of Medicine and Biological Chemistry, then as head of the Department of Molecular Biology and Pharmacology, and now as founding director of the University's interdepartmental,

interdisciplinary Edison Family Center for Genome Sciences and Systems Biology. He is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, the National Academy of Medicine, and the American Philosophical Society. The work of his laboratory has been recognized with a number of awards including the Keio Medical Science Prize, the Louisa Gross Horwitz Prize, the Copley Medal from the Royal Society, the BBVA Foundation Frontiers of Knowledge Award in Biology and Biomedicine, and the Balzan Prize.

#### Microbiome-Directed Complementary Foods for Treating Childhood Undernutrition

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 microbiome are causally related to childhood undernutrition, a devastating global health problem with long-term sequelae, including stunting, neuro–developmental abnormalities, plus metabolic and immune dysfunction, that 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 as well as the experimental and analytic challenges encountered when developing microbiota-directed therapeutics.

### SESSION 1/ BIOGRAPHIES AND ABSTRACTS



#### Moderator: Gabriela Riscuta, M.D., M.S., C.N.S.

Dr. Riscuta is a program director in the Division of Cancer Prevention at the National Cancer Institute (NCI) at the National Institutes of Health (NIH). In this capacity, she identifies gaps in knowledge and future directions of research related to the role of nutrition in cancer risk and progression. She has a special interest in comorbidities, competing risks, and microbiome research in clinical settings. Dr. Riscuta was elected the chair of the NIH-wide Probiotic and Prebiotic Working Group (PPWG), and she is cochairing the Cancer and Aging Interest Group at NCI. Dr. Riscuta graduated from medical school in Bucharest,

Romania and earned her master's degree in human nutrition from the University of Bridgeport.



#### Moderator: R. Dwayne Lunsford, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases

Dr. Lunsford is a program director in the Division of Digestive Diseases and Nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health (NIH). Previously, he was deputy director of the Therapeutic Development Branch, Division of Preclinical Innovation, National Center for Advancing Translational Sciences and director of the microbiology program and coordinator for the small business (Small Business Innovation Research [SBIR]/ Small Business Technology Transfer [STTR]) portfolio at the

National Institute of Dental and Craniofacial Research (NIDCR). He was a founding member of the management team representing NIDCR during the original NIH Human Microbiome Project. Before joining NIDCR in 2007, he had over 20 years of bench-level basic research experience in the public and private sectors. Later positions in the pharmaceutical industry supported new antibiotic discovery programs and preclinical project management (preclinical studies to support investigational new drug applications). Later roles involved the oversight of contracted research on a variety of antimicrobials and countermeasures against biothreat agents. A native Virginian, he received his B.S. (biology) and Ph.D. (microbiology and immunology) degrees from Virginia Commonwealth University in Richmond, Virginia.



#### Rima Kaddurah-Daouk, Ph.D., Duke University

Dr. Kaddurah-Daouk is a graduate of the American University of Beirut Department of Biochemistry, with subsequent training at Johns Hopkins University (worked with Nobel Laureate Hamilton Smith), Massachusetts General Hospital, and the Massachusetts Institute of Technology. She has been a seminal force in the development of applications of metabolomics in the medical field. She cofounded the Metabolomics Society and served more than 4 years as its founding president, helping create a presence and voice for an interactive metabolomics community. She cofounded Metabolon, a leading biotechnology company for applications

in metabolomics, and two other biotechnology companies. With significant National Institutes of Health funding (over 40 grants funded in the past 15 years), she established and leads large consortia (more than 120 scientists from over 30 academic institutions), including the Alzheimer's Disease Metabolomics Consortium (ADMC), which is mapping metabolic failures across the trajectory of Alzheimer's disease (AD), connecting peripheral and central changes, and defining the genetic basis for metabolic alterations and the molecular basis for resilience during aging. Recently, Dr. Kaddurah-Daouk established the Alzheimer Gut Microbiome Project (AGMP), an initiative that includes leadership from the gut microbiome, AD, depression, and metabolomics fields with a mission to define a possible role for the gut microbiome in AD and other neuropsychiatric diseases. Dr. Kaddurah-Daouk leads several initiatives and task groups in precision medicine and has over 140 peer-reviewed scientific publications and more than 60 patents or patent applications.

### Metabolome, Genome, Diet, and Exposome: Toward a Precision Medicine Approach for Probiotic Therapies

It has become increasingly clear that genome, gut microbiome, diet, lifestyle, and environmental exposures can all impact an individual's metabolic state, and this can contribute to health, development of disease, and varied response to treatment. Metabolomics and lipidomics platforms enable measurement of hundreds to thousands of metabolites, providing a readout for net influences on an individual. Metabolomics measurements performed on large population studies showed that each individual has a unique biochemical identity that is stable over years. Connecting metabolome data to other big data creates an unprecedented opportunity to build a precision medicine approach for the subclassification and treatment of human diseases. The National Institute of General Medical Sciences established foundations for "quantitative systems pharmacology," where a multi "omic" approach was predicted to better inform about drug effects and treatment outcomes. With significant funding from the Institute, Dr. Kaddurah-Daouk and colleagues established the Pharmacometabolomics Research Network, which illustrated for the first time how metabolomics data coupled to genetic data can provide great insights about mechanisms of variation of response to 10 classes of commonly used drugs. This same approach can be applied for developing precision probiotic therapies. Dr. Kaddurah-Daouk and colleagues will exemplify the approach and key findings. In addition, they will highlight a large gut microbiome initiative funded by the National Institute on Aging, where they are defining the gut microbiome metabolome and influences on response to treatments.



#### Daniel Merenstein, M.D., Georgetown University

Dr. Merenstein is a professor with tenure of family medicine at Georgetown University, where he also directs family medicine research. Dr. Merenstein has a secondary appointment in the undergraduate Department of Human Science in the School of Nursing and Health Studies. He teaches two undergraduate classes, a research capstone and a seminar class on evaluating evidence-based medical decisions. He has been funded by the National Institutes of Health (NIH), the U.S. Department of Agriculture, foundations, and industry. Dr. Merenstein is the president of the board of directors of the International Scientific

Association of Probiotics and Prebiotics. The primary goal of his research is to provide answers to common clinical questions that lack evidence and to improve patient care. Dr. Merenstein is a clinical trialist who has recruited over 1,900 participants for 10 probiotic trials since 2006. He is an expert on probiotics and antibiotic stewardship in outpatient settings, and he conducts HIV research in a large women's cohort. He sees patients in clinic one day a week. He lives in Maryland with his wife and four boys.

#### Challenges in Precision Probiotic Clinical Trials: Is It Even Possible?

Dr. Merenstein will address the challenges of conducting clinical trials that meet standards and expectations of the U.S. Food and Drug Administration, NIH, and journals. The following aspects of clinical trials will be discussed: number needed to treat, trial registration, the CONSORT (Consolidated Standards of Reporting Trials) guidelines, multiple comparisons, analyzing data in groups as opposed to individual data, blinding, intention to treat, and N-of-1 trials. Dr. Merenstein will discuss how to examine patient-level data and why some people appear to respond to interventions while others do not. He will give real-world examples from his and other researchers' studies and explain the barriers to precision trials under today's expectations. He will provide more questions than answers but hopes this will generate discussion and thought inside NIH about the limitations of precision medicine under the current guidelines and what can be done to promote precision probiotic clinical trials.



#### Mark Haupt, M.D., International Flavors & Fragrances

Dr. Haupt is a board-certified pediatric pulmonologist and currently serves as the chief medical officer at International Flavors & Fragrances (IFF). He completed his medical degree at the Northwestern University Feinberg School of Medicine, after which he completed a residency in general pediatrics at the University of Chicago and served an additional year as chief resident. He returned to Northwestern to complete his pulmonary medicine fellowship at the Ann & Robert H. Lurie Children's Hospital of Chicago. Evaluating nutritional outcomes in cystic fibrosis, particularly regarding pancreatic enzyme replacement therapy, was the focus of his research. Ultimately, he transitioned to the pharmaceutical industry, joining AbbVie, where he worked in a variety of areas before taking on a leadership role in medical affairs. For five years prior to IFF, Dr. Haupt joined an early-stage complex genomics and bioinformatics company focused on precision medicine with an initial focus in pancreatic disease. He joined IFF in November 2021.

#### An Introduction to the Importance of Investigational Product Manufacturing for Probiotic Intervention Trials

From strain selection to good manufacturing practices, specialized testing, formulation, and even packaging, probiotics pose a challenge to deliver the intended dose throughout a study. Challenges include navigating the formats for delivery in different zones or regions, methods of monitoring stability in the field, and strain-specific approaches to determining outcomes. An overview of the important considerations specific to probiotic trials will be discussed, including the following:

- What are the key questions to ask a manufacturer when designing a probiotics trial?
- What must be known to match needs with a supplier?
- What does it take—quality manufacturing, regulatory compliance, and critical success factors from fermentation to shipping.



#### Susan Lynch, Ph.D., University of California, San Francisco

Dr. Lynch is the director of the Benioff Center for Microbiome Medicine and professor of medicine at the University of California, San Francisco. She received her doctoral degree from University College Dublin in Ireland and completed her postdoctoral studies at Stanford University. Her human microbiome research program leverages classical principles of microbial physiology and ecological theory to understand human microbiome genesis, establishment, and influence on human immunity, specifically in the context of childhood allergy and asthma development. Her studies integrate

large multidimensional human microbiome and immune datasets to inform model systems to validate findings and provide a mechanistic understanding of microbial determinants of immune function. These integrative research studies facilitate an "ecosystems to molecules" understanding of the role of the microbiome in defining host health over temporal and spatial gradients. Studies published from Dr. Lynch's laboratory provided some of the first data demonstrating the existence of a gut-airway axis. Dr. Lynch and her colleagues have shown that human infant gut microbiome composition and metabolic output relate to childhood atopy and asthma, identified specific gut microbial genes that predict risk of disease in childhood, and demonstrated that their products modulate immune cell function in a manner consistent with allergic disease development. Leveraging their findings, they have rationally designed a live microbial biotherapeutic to reengineer very early life gut microbiome development and metabolic output to prevent dysfunctional immune maturation in high-risk infants and prevent childhood allergy and asthma.

#### Probiotic Clinical Trials—An Opportunity To Move Toward Precision Microbiome Manipulation

Microbiomes shape human health by regulating the physiology and effector function of mammalian cells. Cellular and molecular communications between microbiomes and human cells govern these interactions. Thus, strategies including probiotic supplementation to manipulate microbiomes and influence microbial-host cross talk represent a growing area of interest in the effort to treat a broad range of human diseases. However, issues related to variability in both the patient populations treated and the probiotic formulations used remain a challenge to the reproducibility of findings. These issues are compounded by a lack of deep functional understanding of the impact of probiotic interventions on microbiome function, molecular productivity, and host immunity. In this talk, Dr. Lynch will propose strategies to address these issues and move the field toward precision microbiome manipulation.



### Sarkis Mazmanian, Ph.D., California Institute of Technology

Dr. Mazmanian is the Luis & Nelly Soux Professor of Microbiology at the California Institute of Technology (Caltech). He was a Phi Beta Kappa graduate from the University of California, Los Angeles, where he also received his doctoral training in microbiology and immunology. He was a Helen Hay Whitney Fellow and an assistant professor of medicine at Harvard Medical School. In 2006, Dr. Mazmanian moved to Caltech to investigate how the gut microbiome impacts development and function of the immune and nervous systems. He has served as principal

investigator on 16 National Institutes of Health–funded grants and numerous foundation and industry awards. His laboratory pioneered the concept that researching the microbiome may lead to development of novel therapies for immunologic and neurological diseases. This work has led to the discovery and validation of drug candidates that are being developed as pharmaceuticals for the treatment of inflammatory bowel disease, autism spectrum disorder, and Parkinson's disease (PD). He is currently focusing on gut-brain research in PD, using animal models and human cell culture systems, as well as via close collaborations with PD clinicians. Dr. Mazmanian has won numerous awards including a Searle Scholarship, Young Investigator of the Year at Harvard Medical School, and the MacArthur Foundation "Genius" award. Most importantly, Dr. Mazmanian has trained numerous students and fellows who have gone on to successful independent careers in science, medicine, and industry.

#### Gut Microbial Metabolites in Human and Animal Behavior

The gut microbiome has been associated with effects on the brain, such as modifying risktaking behaviors and hyperactivity, impacting learning and memory, modulating expression of neurotransmitters, and affecting brain myelination patterns in mice. Studies have reported that the gut microbiome, and certain microbial metabolites, are altered in individuals with autism spectrum disorder (ASD). The microbial metabolite 4-ethylphenyl sulfate (4EPS) was elevated in a mouse model of neurodevelopment and in a large cohort of ASD individuals. Engineering bacteria to selectively produce 4EPS in the gut of mice led to changes in brain activity, functional and structural connectivity in brain regions linked to emotional behavior, and gene expression signatures of altered oligodendrocyte function. Production of 4EPS by the microbiome is associated with increased proportions of immature oligodendrocytes in mice and, accordingly, decreased myelination of neuronal axons in the brain. Furthermore, mice exposed to 4EPS display anxiety-like behaviors, reduced social activity, and decreased vocalization. ASD involves delayed or reduced social communication and repetition of familiar traits and may include social anxiety, irritability/aggression, altered sensory integration, and gastrointestinal symptoms. A pilot human study explored if AB-2004, an oral gut-restricted sequestrant, reduces systemic levels of specific bacterial metabolites elevated in ASD. An open-label Phase 1b/2a clinical trial with 26 adolescent ASD participants confirmed the safety and tolerability of AB-2004, with little to no adverse events reported. Metabolomic analysis was used to validate reduction of key gut-derived metabolites in urine and blood after 8 weeks of treatment. Importantly, drug therapy was associated with improvements in multiple behavioral domains, particularly anxiety and irritability. Preliminary functional magnetic resonance imaging (fMRI) data suggest that oral AB-2004 affects connectivity between specific brain regions implicated in autism.



#### Rajita Menon, Ph.D., Vedanta Biosciences

Dr. Menon is associate director, modeling and statistics at Vedanta Biosciences, leading the analysis of clinical and translational microbiome datasets to optimize bacterial drug cocktails, particularly through the use of statistical and machine learning techniques. Her team develops methods to quantify bacterial strain engraftment, investigate the host response to drug dosing, and identify associations with disease phenotype in human subjects. Dr. Menon completed her doctoral studies in statistical physics at Boston University, where she modeled species interactions in microbial communities and developed a novel statistical method to control for interaction-induced biases in

microbiome data. She was awarded the Hariri Fellowship and the Alvaro Roccaro Prize for her contributions to interdisciplinary computational research. Dr. Menon received her B.S. in physics from Delhi University in New Delhi, India, her M.S. in physics from the Indian Institute of Technology–Delhi, and her Ph.D. in statistical biophysics from Boston University.

### Opportunities and Challenges in Development of Medicines Based on Defined Bacterial Consortia

Manipulation of the gut microbiota via fecal transplantation has shown clinical promise. However, the inherently variable nature of this approach makes it challenging to describe the relationship between drug pharmacokinetics (PK) and pharmacodynamics (PD) and to rationalize clinical successes and failures. Live biotherapeutic products (LBPs) consisting of defined consortia of clonal bacterial isolates have been proposed as an alternative, novel class of therapeutics because of their promising preclinical results in modulating immune and anti-infective responses and their safety profile. Dr. Menon will review challenges and opportunities in clinical development of LBPs based on defined bacterial consortia and discuss a generally applicable framework to quantify the PK and PD of LBPs in humans.

### SESSION 2 BIOGRAPHIES AND ABSTRACTS



# Moderator: Ashley Vargas, Ph.D., M.P.H., R.D.N., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Dr. Vargas, a registered dietitian nutritionist and molecular epidemiologist, is a program director in the Pediatric Growth and Nutrition Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH). Her clinical and research experience focuses on improving the precision of nutrition risk assessment and the application of nutrition therapy to individuals across their lifespan. She has concentrated her research on the relationship between diet and disease that is mediated by the genome and the

microbiome in large human cohorts. Prior to her NICHD appointment, Dr. Vargas served in the Office of Disease Prevention in NIH's Office of the Director, where she led efforts to identify and address major research gaps in the areas of nutrition, physical activity, obesity, and other leading causes and risk factors for death. She also is an alumna of the National Cancer Institute's Cancer Prevention Fellowship Program, where she focused her research on diet, the microbiome, and cancer. Dr. Vargas received her doctoral degree in nutritional science from the University of Arizona, her master's degree in public health from Harvard University, and her bachelor's degree in dietetics from Wayne State University, where she also completed her dietetic training program. She has experience as a clinical R.D.N. in many settings, has served in leadership roles in professional societies, and is a fellow of the Academy of Nutrition and Dietetics.



#### Moderator: Frank A. Hamilton, M.D., M.P.H., M.A.C.G., A.G.A.F., National Institute of Diabetes and Digestive and Kidney Diseases

Dr. Hamilton is board certified in internal medicine, gastroenterology, and preventive medicine and currently serves as director of the Gastrointestinal (GI) Program within the Division of Digestive Diseases and Nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). He is also the project scientist for the NIDDK Gastroparesis Consortium and the Fecal Incontinence Trial and program official for two pancreas trials. He has had a longstanding interest in the impact of behavior and nutrition

on gastrointestinal disorders. Dr. Hamilton received his M.D. from Howard University. He pursued a combined internal medicine residency/preventive medicine program through a

U.S. Public Health Service training program and received his M.P.H. from the Bloomberg School of Public Health at Johns Hopkins University. He obtained further training at the University of Maryland in the Department of Medicine as a GI fellow and then joined the faculty at the University of Maryland. Prior to coming to NIH, he served in the Office of the Surgeon General, where he also served as staff physician on the landmark Health and Human Services Task Force on Black and Minority Health. At NIDDK, Dr. Hamilton has been instrumental in fostering basic and clinical research in gastroenterology, promoting diversity in the makeup of organizations in this field, and eliminating health disparities in colorectal cancer screening. He has published more than 100 peer-reviewed articles and abstracts.



#### Justin Sonnenburg, Ph.D., Stanford University

Dr. Sonnenburg is an associate professor of microbiology and immunology at Stanford University. He received his Ph.D. from the University of California, San Diego and completed a postdoctoral fellowship at Washington University School of Medicine. The goals of Dr. Sonnenburg's research program are to (1) elucidate the basic mechanisms that underlie dynamics within the gut microbiota and (2) devise and implement strategies to prevent and treat disease in humans via the gut microbiota. His long-term objective is to perform mechanistic studies that set the paradigms of how our microbiota may be

incorporated into the emerging vision of precision medicine. His lab investigates the principles that govern microbial community function within the gut using ex-germ-free mice colonized with defined model microbial communities to develop hypotheses that they can pursue within a complex microbiota. The novelty and innovation of Dr. Sonnenburg's research program rely upon the creation and integration of diverse approaches, from imaging to biochemistry to molecular genetics to –omics technologies, in pursuit of fundamental principles within the gut. The synergy of these diverse techniques provides insight into the dynamics of a microbial ecosystem. Dr. Sonnenburg and his colleagues currently combine gnotobiotic mouse models with study of diverse human cohorts, ranging from indigenous populations in Africa and Nepal to dietary intervention trials in cohorts of U.S. residents, including healthy adults and adults with metabolic syndrome. They have recently developed a microbiome-focused metabolomics pipeline that establishes metabolomic profiles of more than 170 gut bacterial strains.

#### **Controlled Engraftment and Abundance of Next-Generation Probiotic Therapies**

The links between the gut microbiome and health, combined with the malleability of this community, suggest that learning the rules for how to manipulate gut microbes may lead to being able to treat and prevent disease. Extensive individuality of the gut microbiome presents a major challenge in reprogramming the gut ecosystem. The fate of exogenous commensal and probiotic strains applied to an established microbiota is variable, largely unpredictable, and greatly influenced by the background microbiota. Gut engraftment and population size of an orally administered bacterial strain can be modulated via provision of resources for the strain of interest. Through administration of a privileged nutrient source,

Dr. Sonnenburg and his team have generated a synthetic metabolic niche and shown uniform integration of an exogenous Bacteroides strain into mice harboring diverse microbiomes, independent of background microbiota. Dietary marine polysaccharides not accessible to other members of the gut community, but utilized by the introduced strain, enable predictable engraftment and boost abundance to high levels. This targeted dietary support overcomes priority exclusion by an isogenic strain and enables replacement of isogenic strains that already inhabit the microbiota. The nutrient-utilization system can be engineered into a naive strain of Bacteroides, and strain abundance may be controlled in the gut by varying dietary polysaccharide input. Data from recent Phase 1 studies support translation of these findings to humans. This work highlights the modularity of metabolic niche space in the gut and suggests resource provision through diet as a powerful factor in reprogramming gut ecosystems.



#### Purna C. Kashyap, M.B.B.S., Mayo Clinic

Dr. Kashyap is professor of medicine and physiology and codirector of the Microbiome and High-Definition Therapeutics program in the Center for Individualized Medicine and director of the germ-free mouse facility at Mayo Clinic, Rochester, Minnesota. His gut microbiome laboratory is interested in understanding the complex interactions between diet, the gut microbiome, and host physiology and strives to move the field beyond associations of the microbiome with different diseases to defining the functional role of gut microbes in regulating host physiology. The laboratory uses germ-free mouse

models in conjunction with measures of gastrointestinal physiology in vitro and in vivo to investigate effects of gut microbial products on host gastrointestinal function. In parallel, they use a systems approach incorporating multiomics, patient metadata, and physiologic tissue responses in human studies to aid in discovery of novel microbial drivers of disease. The overall goal of the program is to develop novel microbiota-targeted therapeutic agents, such as genetically engineered microbes, that will restore altered microbial functions in diseases such as irritable bowel syndrome. Dr. Kashyap's research is driven primarily by his clinical practice, which is focused on patients with gastrointestinal motility disorders. Dr. Kashyap has published over 80 peer-reviewed articles in journals including *Cell, Cell Host Microbe, Science Translational Medicine, Nature Communications,* and *Gastroenterology*. He serves on the council and the research committee of American Gastroenterology Association, in editorial roles for *Gut Microbes* and *Neurogastroenterology and Motility,* and as an ad hoc reviewer on National Institutes of Health study sections.

#### Multiomics to Mechanisms: The Road to Microbiome-Driven Precision Medicine

The current treatment paradigm of one-size-fits-all does not consider interindividual variability in an individual's exposome—including diet, lifestyle, and environment— and genetics—including host and microbial genes—which underlie the pathogenesis, susceptibility, and outcomes of most chronic diseases to varying levels. While there has been a significant interest in host genetics since, with sequencing of the host genome, there

is increasing realization that microbial genes also contribute to several pathophysiologic mechanisms. To move toward a personalized medicine approach, there is a need to consider nonlinear contributions from patient genetics, microbiome, and exposome. In this presentation, Dr. Kashyap will discuss the contribution of the microbiome in the pathophysiology of functional gastrointestinal disorders like irritable bowel syndrome, in the context of host omics and physiological responses, as well as environmental factors. This approach can facilitate personalized treatment strategies by providing more meaningful mechanism-based stratification.



#### Gianna Hammer, Ph.D., Duke University

Dr. Hammer started her laboratory in 2013 at Duke University and is currently in the process of moving to the University of Utah, Salt Lake City. She received her Ph.D. from the University of California, Berkeley where, under the mentorship of the late Dr. Nilabh Shastri, she described the seminal contributions of aminopeptidase ERAAP in the generation of peptides for MHC class I molecules. Her postdoctoral studies with Dr. Averil Ma focused on dendritic cell-mediated control of immune homeostasis and the roles of the NF-kB suppressor A20 in this process. Her lab now focuses on dynamics between host and microbe at mucosal

barriers, with ongoing research programs investigating immune dynamics in the healthy gut, the inflamed gut, the pathogen-infected gut, and colorectal cancer. For her contributions to science, Dr. Hammer has been named a Damon Runyon Cancer Research Fellow, a Pew Scholar in the Biomedical Sciences, a V Scholar for Cancer Research, and a Burroughs Wellcome Fund Investigator in the Pathogenesis of Infectious Disease. In addition to her commitment to scientific excellence, Dr. Hammer is committed to mentorship of the next generation of scientific leaders; in addition to the trainees in her lab, she also mentors select students and postdocs, particularly underrepresented minorities, outside her institution. Dr. Hammer has served on the strategic planning committee for Duke's faculty committee for antiracism and equity and as an invited speaker at a Capitol Hill briefing focused on the critical need for diversity among academic faculty.

### Keeping It "Old School"—The Influence of the Microbiome on Responses, Regulation, and Metabolic Rewiring of Long-Lived, Fetal-Derived Immune Cells

Education has a crucial influence, yet most cannot remember their teachers' names, let alone the name of their very first teacher. By contrast, immune cells value education so highly that some teachers are kept forever—even some that existed before birth. These "old school" educators are fetal-derived and include innate-like IL-17 producing  $\gamma\delta$  T cells ( $\gamma\delta$ 17). How fetal-derived  $\gamma\delta$ 17 cells respond to microbiota or probiotics and how these responses affect the behaviors of other host cells are largely unknown. Still, their discovery is important because they may have life-long consequences for disease or probiotic-based interventions. Dr. Hammer and her team have found that microbiota-mediated regulation of  $\gamma\delta$ 17 cells is binary, wherein microbiota upregulate IL-17-production and concomitant expression of the inhibitory receptor programmed cell death protein 1 (PD-1). Microbiotadriven PD-1 inhibits natural IL-17 production by  $\gamma\delta$ 17 cells, thus linking microbiota to the simultaneous activation and suppression of  $\gamma\delta$ 17 cell functions. These two modules are dynamic, wherein both PD-1 and IL-17 are downregulated upon microbiota depletion and concomitantly upregulated during microbial dysbiosis and intestinal inflammation. These functional changes in inflammation are marked by a dramatic increase in lipid uptake, thus linking augmented behaviors of  $\gamma\delta$ 17 cells to metabolic rewiring of these fetal-derived cells within the intestine. Findings highlight fetal-derived  $\gamma\delta$ 17 cells as long-lived responders sensitive to dynamic changes in the microbiome, including those introduced by probiotic-based interventions. The setpoint of PD-1 and lipid uptake on fetal-derived  $\gamma\delta$ 17 cells and the long-term imprinting of these by pathogen infection or inflammatory events are likely to be critical regulators of how probiotics impact host physiology, as well as interpersonal variation of probiotic-based interventions.



#### Jun Huh, Ph.D., Harvard University

Dr. Huh obtained his Ph.D. from the California Institute of Technology and conducted his postdoctoral work at New York University School of Medicine as a recipient of the Jane Coffin Childs Memorial Fund Fellowship. He received a National Institutes of Health Pathway to Independence Award and a Smith Family Award for Excellence in Biomedical Research. Dr. Huh was named a 2015 Searle Scholar and a 2016 Pew Scholar. In 2019, Dr. Huh was selected as an investigator in the pathogenesis of infectious disease by the Burroughs Wellcome Fund. Dr. Huh's laboratory studies mechanisms by which maternal

inflammation leads to neurodevelopmental disorders in offspring. In mice, pregnant females infected with viruses give birth to offspring that exhibit behavioral phenotypes that resemble the symptoms of autism spectrum disorder. Dr. Huh's lab has shown that the bacterial community in the maternal gut plays an essential role in this model by promoting the differentiation of Th17 cells. Dr. Huh is also interested in identifying host- and bacteria-derived factors that regulate inflammation in the mammalian gut. Lastly, Dr. Huh aims to identify novel agents to control inflammation by modulating immune receptor activities to treat inflammatory and neurological disorders.

#### Microbial Metabolites of Bile Acids in Controlling Host Immune Cell Function

Maintaining an equilibrium between inflammatory Th17 cells and anti-inflammatory regulatory T cells (Tregs) is critical to support intestinal barrier function and tissue homeostasis. Nuclear hormone receptors (NhRs) have been shown to play crucial roles in the development and function of key immune cells, including Th17 and Treg cells. Based on prior work, Dr. Huh and his team hypothesize that microbial metabolites of bile acids bind to host NhRs and modulate T cell differentiation and function. They identified human gut bacteria and corresponding enzymes that produce immune-modulatory bile acids using mass spectrometer-based screening approaches. They showed that immune-modulatory bile acids with inflammatory bowel disease. Overall, the data suggest that bacterially produced bile

acids regulate Th17 and Treg cell differentiation and function, which may be relevant to the pathophysiology of inflammatory disorders such as inflammatory bowel disease.



### Amir Zarrinpar, M.D., Ph.D., University of California, San Diego

Dr. Zarrinpar is an assistant professor of gastroenterology at the University of California, San Diego, where he also received his M.D. and Ph.D. He is a physician scientist whose primary research is focused on how the gut microbiome and disrupted circadian rhythms conspire to cause multiple physiological disorders, including obesity and type 2 diabetes. As a postdoctoral fellow at the Salk Institute, he helped discover a new behavior modification paradigm that helps prevent obesity called time-restricted feeding. This was followed by studies investigating circadian

fluctuations in the gut microbiome and their role in metabolism, as well as the effect of microbiome depletion on host glucose homeostasis. He has demonstrated that the luminal environment is highly dynamic, with dramatic shifts within hours, and heavily influenced by diet and feeding patterns. He has since been focused on the function of the microbiome, rather than the composition, which is more relevant to host physiology. To test these new functions his laboratory developed a new approach of using engineered native bacteria to investigate the functional role of the gut microbiome on host physiology. These approaches allow them to devise novel microbiome-mediated therapeutic approaches with curative intent for many genetic and chronic medical disorders while accounting for tremendous diet- and circadian-based intra- and interindividual variability. Dr. Zarrinpar is a recipient of the American Association for the Study of Liver Diseases Liver Scholar Award and American Gastroenterological Association Microbiome Junior Investigator Award.

#### The Microbiome and Time: Using Engineered Bacteria To Understand Microbiome-Circadian Relationships

Although many aspects of microbiome studies have been standardized to improve experimental replicability, none account for how the daily diurnal fluctuations in the gut lumen cause dynamic changes in microbiome composition and function. These daily oscillations are necessary for normal circadian rhythms and metabolic homeostasis. Dietinduced obesity (DIO) perturbs microbial oscillations and causes peripheral circadian disruption. Time-restricted feeding (TRF) maintains circadian synchrony, particularly in specific bacterial functions involving bile acid modifications, and protects against DIO. To better understand the relationship between gut microbial functions and host metabolism/ circadian rhythms, Dr. Zarrinpar and his team developed engineered native bacteria, which can engraft in conventionally raised wild-type mice after a single treatment, change the luminal environment, affect host physiology, and reverse disease for prolonged periods of time. By using engineered native bacteria, they determined the role of circadian dysregulation in age-related dysmetabolism and how bacterial functions can be manipulated to ameliorate this problem. Overall, a better understanding of the diurnal oscillations of the luminal environment can help inform live bacterial therapeutic design and identify key functions that can then be manipulated to preserve host health.



### Sharon M. Donovan, Ph.D., R.D., University of Illinois, Urbana-Champaign

Dr. Donovan received her Ph.D. in nutrition in the laboratory of Bo Lönnerdal at the University of California at Davis. She completed a postdoctoral fellowship at the Stanford University School of Medicine before joining the faculty in the Department of Food Science and Human Nutrition at the University of Illinois, where she is currently professor and Melissa M. Noel Endowed Chair in Nutrition and Health. In 2020, she was named the inaugural director of the Personalized Nutrition Initiative at the University of Illinois. Her laboratory conducts basic and translational research

in the area of pediatric nutrition. Ongoing work is focusing on nutritional approaches to optimize the development of the gut microbiome and gut, immune, and cognitive development in infants. Dr. Donovan has over 240 peer-reviewed publications and has garnered over \$35M in grant support from the National Institutes of Health, U.S. Department of Agriculture, foundations, and the food and pharmaceutical industries. She was elected to the National Academy of Medicine in 2017 and served on the 2020–2025 Dietary Guidelines for Americans Advisory Committee.

#### Noninvasive Interrogation of Host-Microbiome Crosstalk in the Human Infant

The first 1,000 days of life are essential for establishing the gut microbiome and programming lifelong health through diet-host-microbe interactions. Dr. Donovan's goal is to understand how early life nutrition shapes the composition and function of the gut microbiome and its association with short- and long-term health outcomes, including intestinal development. However, investigating intestinal development in healthy human infants has been limited by the lack of non-invasive approaches. To meet this need, Dr. Donovan and her team developed a non-invasive method for assessing intestinal mRNA expression using exfoliated epithelial cells (exfoliome) in stool. In the piglet, they demonstrated that the exfoliome contains gene markers representing a diverse array of cell types arising from both the small and large intestine and genes mapped to nutrient absorption and transport and immune function. Using this approach, they demonstrated that gene signatures differ between breastfed and formula-fed infants and between preterm and term infants. Variation in both host mRNA expression and the microbiome phylogenetic and functional profiles was observed between breastfed and formula-fed term infants. Interdependent relationships between host exfoliome and bacterial metagenomicbased profiles were investigated using multivariate statistical analyses. Gut microbiota metagenome virulence characteristics concurrently varied with immunity-related gene expression in host cells, indicating potential transgenomic crosstalk between the formulafed and breastfed infants. Thus, the exfoliome represents a robust reservoir of information in which to longitudinally assess intestinal development, host-microbe interactions, and responses to dietary and probiotic interventions.



#### Steven D. Townsend, Ph.D., Vanderbilt University

Dr. Townsend is a professor in the Department of Chemistry at Vanderbilt University. He was born and raised on the east side of Detroit. He received his undergraduate degree from Oakland University, where he completed 4 years of research on the synthesis of nucleoside radical precursors with Professor Amanda Bryant Friedrich. From there he matriculated to Vanderbilt University, where he studied organic chemistry, working on the synthesis of bielschowskysin under the mentorship of Professor Gary Sulikowski. He completed his education at Sloan Kettering Institute and Columbia University with Professor

Sam Danishefsky, where he worked on the total synthesis of erythropoietin, parathyroid hormone-related protein (PTHrP), peptide ligation, and Diels-Alder methodology. In 2014, he established an independent program at Vanderbilt University, where his group leverages organic chemistry to address problems in human health, particularly in the areas of human milk science, antimicrobial agents, and chemotherapeutics. Dr. Townsend's team has been honored with a number of awards, including most recently the Sloan Research Fellowship, the Camille Dreyfus Teacher-Scholar Award, the David Y. Gin New Investigator Award from the American Chemical Society, the Ruth A. Lawrence Investigator Award for Excellence in Human Milk Science, and the *Chemical and Engineering News* Talented 12. Steve's dedication to education is highlighted by his Jeffrey Nordhaus Award for Excellence in Undergraduate Teaching.

#### Application of 2'-Fucosyl Lactose in Preventing Intestinal Injury

Human milk oligosaccharides (HMOs), the third most abundant solid component in human milk, enable infant health and wellness. Dr. Townsend and his team have recently taken an interest in exploring the health effects of HMOs in adulthood. Accordingly, they have reported that 2'-fucosyllactose (2'-FL) protects intestinal epithelial cells (IECs) against chemotherapy-induced injury. This study generated two novel findings, the direct effect of 2'-FL on epidermal growth factor receptor activation in IECs and its involvement in prevention of intestinal inflammation in adulthood. Dr. Townsend and his team concluded that 2'-FL might serve as a preventive strategy for individuals with high risk of developing inflammatory bowel disease. The aim of this presentation is to showcase how HMOs, via related mechanisms, can prevent inflammation in mucositis and colitis.



#### Liping Zhao, Ph.D., Rutgers University

Dr. Zhao is currently the Eveleigh-Fenton Chair of Applied Microbiology at the Department of Biochemistry and Microbiology, School of Environmental and Biological Sciences and director of the Center for Nutrition, Microbiome, and Health of the New Jersey Institute for Food, Nutrition, and Health, Rutgers University. He is a fellow of the American Academy of Microbiology and a senior fellow of the Canadian Institute for Advanced Research. He serves on the Scientific Advisory Board for the Center for Microbiome Research and Education of the American Gastroenterology Association. His team has

pioneered the approach of applying metagenomics-metabolomics integrated tools and dietary intervention for systems understanding and predictive manipulation of gut microbiota to improve human metabolic health. Following the logic of Koch's postulates, Dr. Zhao has found that endotoxin-producing opportunistic pathogens overgrowing in the obese human gut can induce obesity, fatty liver, and insulin resistance when monocolonized in germ-free mice via the endotoxin-TLR4 pathway as the initiating molecular crosstalk. His clinical trials published in *Science* and *EBioMedicine* showed that high dietary fiber modulation of gut microbiota can significantly alleviate metabolic diseases including a genetic form of obesity in children and type 2 diabetes in adults. Science featured a story on how Dr. Zhao combines traditional Chinese medicine and gut microbiota study to understand and fight obesity (http://science.sciencemag.org/content/336/6086/1248).

#### Reference-Free and Guild-Based Approach for Discovering Novel Probiotic Bacteria With Ecological Competency

Gut microbiome is not the "-ome of all microbial genes" but the "biome of all microbes" living in human gut. As a microbial ecosystem, microbiome is a complex adaptive system in which strains, as the most basic building blocks, organize themselves into a higher-level structure called guilds. Guilds are functional units that consist of strains with diverse taxonomic backgrounds yet work together to contribute to community-level emergent functions relevant to human health. Co-abundance analysis of amplicon sequence variants (ASVs) of 16S rRNA gene or high-quality draft genomes assembled from metagenomic datasets (metagenome-assembled genomes, MAGs) can help identify key guilds that show correlation between ecological behavior and host phenotypes. Different from taxon-based and genecentric approaches, this strategy does not need prior knowledge in databases. Coupled with microbiome-targeted nutritional interventions, this approach may discover novel beneficial bacteria with ecological competency as candidates for next generation therapeutic probiotics.



#### Andrew Goodman, Ph.D., Yale University

Dr. Goodman is the C.N.H. Long Professor of Microbial Pathogenesis at Yale University School of Medicine and director of the Yale Microbial Sciences Institute. He received his undergraduate degree in ecology and evolutionary biology from Princeton University and his Ph.D. in microbiology and molecular genetics from Harvard University, and he completed postdoctoral training at Washington University. His lab uses microbial genetics, gnotobiotics, and mass spectrometry to understand how the gut microbiome contributes to drug metabolism. The Goodman lab works to identify and characterize

microbiome-encoded drug metabolizing enzymes and to define how these microbial activities contribute to drug and drug metabolite exposure in the gut and in circulation. The lab's contributions have been recognized by the National Institutes of Health Director's New Innovator Award, the Pew Foundation, the Dupont Young Professors Award, the Burroughs Wellcome Foundation, the Howard Hughes Medical Institute Faculty Scholars Program, the American Society for Pharmacology and Experimental Therapeutics John J. Abel Award, and the Presidential Early Career Award in Science and Engineering.

#### Microbiome Contributions to Drug Metabolism

Oral medicinal drugs can exhibit incomplete absorption in the upper gastrointestinal (GI) tract or reach the gut after enterohepatic circulation. In these circumstances, drugs encounter enormous densities of commensal microbes, suggesting that microbiome-targeted interventions may be a means to modulate exposure to drugs and drug metabolites in the GI tract and in circulation. However, the contribution of the microbiome to these processes is largely unexplored. Dr. Goodman will describe examples that suggest that gut microbial activity can be responsible for a significant portion of systemic exposure to a toxic drug metabolite, even if the drug exhibits high bioavailability, if the same metabolite is readily produced by hepatic extracts in vitro, and if drug metabolite levels are low in feces. Dr. Goodman will also introduce efforts to explore the spectrum of microbiome-encoded drug metabolizing activities and to identify microbial genes that predict the capacity of an individual's gut microbiome to metabolize a drug.

### OPENING REMARKS



#### Joseph M. Betz, Ph.D., Office of Dietary Supplements

Dr. Betz is the acting director of the Office of Dietary Supplements (ODS) at the National Institutes of Health. He joined ODS in 2002 as the first director of the Analytical Methods and Reference Materials (AMRM) program. As AMRM director, he oversaw several large intra- and extragovernmental initiatives with the goal of providing stakeholders with rugged, validated analytical methods and reference materials for measuring natural products in research, industrial, and regulatory settings. Prior to joining ODS, Dr. Betz was vice president for scientific and technical affairs at the American Herbal Products Association (AHPA).

Before serving at AHPA, he worked for many years at the U.S. Food and Drug Administration (FDA), beginning when he joined the Division of Natural Products at FDA's Center for Food Safety and Applied Nutrition for his postdoctoral work. Later, he accepted a full-time job as a research chemist at FDA, where he remained for 12 years. Dr. Betz is an adjunct associate professor in the Department of Pharmacology and Physiology at the Georgetown University School of Medicine and in the Department of Cell Biology and Biotechnology at his alma mater, the Philadelphia College of Pharmacy and Science, now called the University of the Sciences (USciences). A native of Philadelphia, Dr. Betz earned a bachelor's degree in biology at USciences and a master's degree in marine and environmental science at C.W. Post/Long Island University. He earned a Ph.D. in pharmacognosy at USciences.

### KEYNOTE SPEAKER



#### Gary D. Wu, M.D., Perelman School of Medicine, University of Pennsylvania

Dr. Wu is the Ferdinand G. Weisbrod Professor in Gastroenterology at the University of Pennsylvania's Perelman School of Medicine. He is the director for basic research in the Division of Gastroenterology and Hepatology, director of the Penn Center for Nutritional Science and Medicine, and codirector of both the National Institutes of Health (NIH) Center for Molecular Studies in Digestive and Liver Disease and the PennCHOP Microbiome Program. He was the inaugural director and chair of the Scientific Advisory Board for the American Gastroenterological

Association's Center for Gut Microbiome Research and Education and is an elected member of both the American Society for Clinical Investigation and the Association of American Physicians. Research in the Wu lab currently focuses on the impact of diet on the gut microbiome and its relationship to several aspects of host metabolism including nitrogen balance, intestinal oxygen regulation, and epithelial intermediary metabolism.

### The Gut Microbiome in IBD as a Prototype for the Opportunities and Challenges in the Development of Precision Probiotics: The Next Steps

Tremendous advances in technology have propelled modern microbiome research, leading to seminal discoveries over the past three decades, where mechanistic studies in model systems have shown significant effects of microbes on mammalian physiology and where association studies implicate a role for the microbiota in human health and disease. The prospects of developing the next generation of probiotics (also known as live biotherapeutic products, or LBPs) to prevent and/or treat disease are promising. Fundamentally important will be the translation of conceptual advances in animal models to human physiology where inter-subject variability combined with small effect sizes will be challenging to address. In this talk, Dr. Wu will use concepts relevant to the pathogenesis and treatment of inflammatory bowel disease (IBD) as a paradigm to highlight some of the next steps in the development of precision probiotics that must take into account the compositional community dynamics of the gut microbiota as well as the environmental impact on its composition and function. The biologically active component of a therapeutic will be discussed, including the viability of the microorganism and its metabolic function, either natural or engineered. Finally, practical considerations about the development of the LBPs for disease treatment will be discussed from the lens of currently available therapeutic strategies for IBD. Throughout this presentation, the work and expertise of the speakers in Session 3, "Next generation probiotics-new strain identification and development," and Session 4, "Emerging technologies for precision probiotics," will be highlighted.

### SESSION 3 BIOGRAPHIES AND ABSTRACTS



### Moderator: Padma Maruvada, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases

As a program director in the Division of Digestive Diseases and Nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Dr. Maruvada manages the Nutrient Metabolism, Status, and Assessment program and the Clinical, Behavioral, and Epidemiological Obesity Research programs. Her grants portfolio also includes research projects on diet, microbiome, and host interactions. She co-leads the Office of Nutrition Research's diet, microbiome, and host interrelationships implementation working group. Dr. Maruvada is involved

in a variety of Common Fund-supported programs. She serves as project scientist for the Metabolomics Consortium Coordinating Center for the metabolomics program that supports a national consortium and provides resources and infrastructure for metabolomics technologies for promoting their application in biomedical research. She serves as one of the program directors for the Molecular Transducers of Physical Activity (MoTrPAC) program, which was established to map the molecular signatures of physical activity. She is also involved with the recently launched Common Fund Nutrition for Precision Health program to develop algorithms that predict individual responses to food and dietary patterns. She serves as the project scientist for the Metabolomic and Clinical Analysis Center and as a program officer for the Microbiome and Metagenome Centers.



### Moderator: Ryan Ranallo, Ph.D., National Institute of Allergy and Infectious Diseases

Dr. Ranallo is a program officer in the Division of Microbiology and Infectious Diseases (DMID) at the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH). He received a B.S. degree in microbiology from Ohio University and a Ph.D. in biochemistry and molecular biology from Colorado State University. He completed a postdoctoral fellowship at the National Cancer Institute, in the laboratory of Carl Wu. In 2002, Dr. Ranallo transitioned to the Walter Reed Army Institute of Research, where he successfully designed,

constructed, and manufactured live attenuated *Shigella* vaccines. In 2012, he transitioned to NIAID for a career in scientific administration, where he manages a portfolio of grants, contracts, and clinical trials involving *Clostridium* spp., botulinum neurotoxin, and the gut microbiome. Dr. Ranallo is the NIAID point of contact for translational microbiome research and the cochair of the Trans-NIH Microbiome Working Group, which provides a forum for coordinating NIH extramural research activities related to the human microbiome.



#### Julia Oh, Ph.D., The Jackson Laboratory

Julia Oh received her B.A. from Harvard University and her Ph.D. in genetics from Stanford University and completed her postdoctoral training at the National Institutes of Health. Now an associate professor at the Jackson Laboratory, Dr. Oh is a microbiome expert with a focus on combining highresolution computational reconstructions of the microbiome with synthetic biology to devise innovative approaches to create new therapeutic interventions and investigate the underlying ecology of skin microbial communities.

### From Metagenomes to Therapeutics: The Human Skin Microbiome

The human skin harbors an abundant microbial ecosystem with bidirectional metabolic exchanges supporting symbiotic and commensal functions. Sequence-based analysis of the microbial community structure and organization of the human microbiome has yielded valuable insight into the microbial diversity and function of its different body niches. Metagenomic analyses of the diverse skin sites in healthy humans demonstrate that contrasting forces of the skin's biogeography and individual characteristics shape the skin microbiome and the dynamics of its bacteria, fungi, and viruses. However, Dr. Oh and colleagues have shown that shifts in the ecological properties of the skin microbiome are significantly associated with skin disease, disease severity, and other physiologic host factors such as age or primary immunodeficiency. They have deeply probed skin microbiome composition and function at subspecies resolution, focusing on a keystone skin microbe, Staphylococcus epidermidis. They uncovered an extraordinary within-individual diversity at the strain level that they found can suppress population-level virulence of this opportunistic microbe. They complemented this strain-level genomic investigation with CRISPR interference (CRISPRi) and transcriptomic profiling to probe S. epidermidis gene function in skin environments. Finally, they investigated how these diverse S. epidermidis strains program the skin milieu in 3D skin cultures, identifying strain-specific immune and skin signatures. Taken together, their results highlight the genetic and functional diversity of the skin microbiome at the strain level. Strain diversity is an emerging frontier of understanding host-microbiome interactions and therapeutic discovery, as it harbors a tremendous amount of individual- and disease-specific genetic and phenotypic diversity.



#### June L. Round, Ph.D., University of Utah

Dr. Round is an associate professor in the Division of Microbiology and Immunology at the University of Utah and a member of the Huntsman Cancer Institute. Her graduate studies at the University of California, Los Angeles, in the laboratory of M. Carrie Miceli, were focused on T cell signaling events leading to activation of immune responses. Her postdoctoral studies were conducted at the California Institute of Technology in the laboratory of Sarkis Mazmanian. She was supported by the Jane Coffins Child Fellowship and published works on how commensal microbes induce intestinal health. This training has provided her expertise in mucosal immunology, use of gnotobiotic mouse model systems, and isolation and culture of anaerobic gut microbes. Upon starting her own laboratory at the University of Utah, she was the recipient of the Edward Mallinckrodt Fellowship and Pew Biomedical and Packard Scholar Awards, as well as National Science Foundation Faculty Early Career Development (CAREER) and National Institutes of Health Innovator Awards. Her laboratory has also been supported by the American Asthma Foundation, the Crohn's and Colitis Foundation, the Helmsley Foundation, and the W.M. Keck Foundation. Her laboratory focuses on how the immune system and the commensal microbiota interact to maintain intestinal homeostasis. Her laboratory works with bacterial, fungal, and viral members of the microbiota.

#### Microbiota-Immune Interactions That Promote Intestinal Health

While the immune system is classically thought to recognize foreign microbes and eradicate them from the body, it is now known that it also functions to shape the composition and function of the microbiota. However, the mechanisms by which this occurs are still under investigation. Dr. Round and her team have shown that antibodies within the gut select for microbes that prevent obesity and metabolic syndrome. They are currently identifying specific strains that confer leanness and the mechanisms by which the strains prevent disease. Dr. Round and her team have also shown that intestinal antibodies can control invasive epitope expression on gut fungi to prevent colitis. These immune responses do not eliminate the organism, rather they cause downregulation of proteins that exacerbate disease. This natural immune response can be exploited using a vaccination approach to prevent intestinal inflammation. Thus, by studying how the immune system interacts with the microbiota, it is possible to identify relevant microbes and their products that can be used therapeutically.



### Jan Peter van Pijkeren, Ph.D., University of Wisconsin–Madison

Dr. van Pijkeren is an associate professor at the Department of Food Science, chair of the food science graduate program, and an executive member of the Food Research Institute at the University of Wisconsin–Madison. Dr. van Pijkeren received a B.S. in biotechnology from the Noorderlijk Hogeschool Leeuwarden and an M.S. in biology from Leiden University, both in the Netherlands. He joined the laboratory of Dr. Paul O'Toole at University College Cork, Ireland, where he completed his Ph.D. training in microbiology. During his postdoctoral training at the Cork

Cancer Research Center, Ireland, Dr. van Pijkeren developed *Listeria monocytogenes* as a DNA delivery vehicle. After completing his second postdoctoral training under Dr. Robert Britton at Michigan State University, he started his own laboratory in 2013. Dr. van Pijkeren developed various genome editing tools for use in undomesticated lactobacilli, which are essential to pursue his long-term research goals. Studies in the van Pijkeren laboratory focus mostly on the gut symbiont species *Limosilactobacillus reuteri*, until recently known as

Lactobacillus reuteri. His research team aims to unravel the molecular mechanisms by which a gut symbiont interacts with its host and by which diet drives the interaction between a gut symbiont and its phages, and — finally — to exploit the acquired knowledge to develop next-generation probiotics for use in human medicine.

#### **Bioengineered Probiotics To Deliver Therapeutics**

Limosilactobacillus reuteri, until recently known as Lactobacillus reuteri, has evolved to thrive in the vertebrate gastrointestinal tract. Select strains have probiotic properties, and various genome editing tools have been developed for use in L. reuteri. In addition, compared to other Gram-positive bacteria, L. reuteri has a relatively low mutation rate, which is expected to contribute to genetic stability. Collectively, this makes L. reuteri an attractable vehicle to produce and deliver therapeutic molecules. The van Pijkeren laboratory engineers L. reuteri to accumulate recombinant proteins inside the cell. Native intracellular viruses are activated during gastrointestinal transit and lyse recombinant L. reuteri, releasing therapeutic protein into the environment. Using this approach, Dr. van Pijkeren and his team engineered L. reuteri to produce and release the cytokine interleukin-22, which has proven successful in ameliorating disease in preclinical models of alcohol-induced liver disease and irradiation-induced intestinal damage. Critical next steps in developing the L. reuteri therapeutic delivery system are tight control of lysis and thus therapeutic release. Thus far, proof-of-concept to prime production of viruses in vitro has been established, leading to a significant increase of therapeutic release and more robust lysis during gastrointestinal transit. Also, experiments are ongoing toward preventing longterm colonization of the genetically modified organism. To this end, Dr. van Pijkeren and his team inactivated nine genes hypothesized to affect colonization. Compared to the wild-type strain, the nonuple mutant has reduced adhesive ability to intestinal enteroid cells while gastrointestinal survival in mice is not affected. Projecting forward, successful completion of planned safety and efficacy studies in nonhuman primates paves the way for clinical trials.



### Tami Lieberman, Ph.D., Massachusetts Institute of Technology

Dr. Lieberman is an assistant professor at the Massachusetts Institute of Technology (MIT), in the Institute for Medical Engineering and Sciences and the Department of Civil and Environmental Engineering, and an associate member of both the Broad Institute and the Ragon Institute. Dr. Lieberman received a B.A. in biological sciences, with a minor in mathematics, from Northwestern University and a Ph.D. in systems biology from Harvard University. As a graduate student in Roy Kishony's laboratory, she studied bacterial evolution during human infections at the whole

genome level and developed experimental tools for understanding the evolution of antibiotic resistance. She then completed a postdoctoral fellowship in Eric Alm's laboratory at MIT, where she used the computational tools developed in her Ph.D. dissertation to discover the first evidence that bacteria in the gut microbiome change via adaptive mutations even

during health. The Lieberman lab is continuing to develop new tools to track and model within-person bacterial evolution, with a focus on the skin microbiome, toward revealing mechanistic understanding of community assembly in real human microbiomes and the impact of in-microbiome mutations for health and disease.

#### Inferring In-Human Commensal Biology by Reconstructing Within-Person Bacterial Evolution

There is an enormous potential for evolution within each of our microbiomes, with billions of new mutations being created each day. In this talk, Dr. Lieberman will highlight the power of tracking within-person evolution for understanding microbiome community assembly, identifying bacterial genes critical to in vivo survival, and understanding host-microbe interactions.



### Erwin G. Zoetendal, Ph.D., Wageningen University & Research

Dr. Zoetendal is associate professor at the Laboratory of Microbiology of Wageningen University & Research (MIB-WUR). He studied biology at the University of Groningen. Afterwards, he earned his Ph.D. (2001) with research focusing on molecular characterization of bacterial communities in the human gastrointestinal tract at MIB-WUR. After postdoctoral research positions at the University of Kuopio (Finland) and the University of Illinois at Urbana-Champaign, Dr. Zoetendal returned as a postdoctoral fellow at MIB-WUR and became an associate professor in 2015.

Dr. Zoetendal's research focuses on the role of the microbiome in the intestine and how this is related to diet and health. He uses a wide variety of culture-independent methods to characterize the microbiota composition and activity in cohorts of healthy and compromised subjects in combination with dedicated in vitro laboratory experiments using fecal slurries and defined cultures with the aim of understanding the ecology of the intestinal ecosystem. Dr. Zoetendal's research has been funded by various national and international funding agencies. Dr. Zoetendal is a well-recognized expert in intestinal microbiology and was one of the pioneers in using 16S ribosomal RNA technologies to study the intestinal microbiota in humans. He has over 100 publications with an H-index of 72 (March 2022, Google Scholar). He has given numerous lectures, including the Rome Foundation AGA Institute Lecture at Digestive Disease Week 2010. He is an elected member of the Rome Foundation and honorary guest professor at Nanjing Agricultural University (China).

#### Novel Probiotics From Our Microbiome

Our intestine harbors a complex ecosystem, often abbreviated as microbiome, that plays a crucial role in our health. The past decades have been characterised by an explosive increase in studies focusing on the intestinal microbiome in health and disease. This increase has been largely facilitated by fast developments and the application of high-throughput culture-independent technologies to study the microbiome's bacterial inhabitants, notably, approaches using 16S ribosomal RNA or its encoding gene as a

marker for bacterial identification. Probiotics, defined as live microorganisms that when administered in adequate amounts confer a health benefit on the host, have frequently been used to study their potential as microbiota-targeted treatment for various diseases and disorders. So far, most probiotics are food-derived microorganisms that are mostly belonging to the genera *Lactobacillus* and *Bifidobacterium*. However, given the fact that recent studies have shown that our own microbiome can harbor bacteria with beneficial health potential, there is a need for human-derived probiotics, also often defined as next generation probiotics (NGPs). Recent examples of potential NGPs include strains belonging to *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*. However, the isolation and characterization of NGPs comes with several challenges with respect to cultivation, safety, and efficacy screening. Dr. Zoetendal will focus on strategies to isolate potential NGPs from our microbiome and how to tackle these challenges using examples of ongoing research within the Novobiome project.



### Rustem F. Ismagilov, Ph.D., California Institute of Technology

Dr. Ismagilov is a professor at the California Institute of Technology. He received his Ph.D. in chemistry from the University of Wisconsin–Madison and did his postdoctoral research at Harvard. His research is focused on global health, including rapid diagnostics of infectious diseases. He is also focused on understanding the interplay among gut microbes, food, and biophysics. His lab develops quantitative technologies for ultrasensitive measurements of microbes in host-rich environments. A particular area of focus is the small intestine and mucosa-associated microbes.

### Small Intestine and Microbes Are Central to Human Health, but Understanding Their Role Requires Quantitative Tools Applied to Human (Not Animal) Samples

Analyses of the gut microbiome must examine human small intestinal samples. The small intestine is where the immune system is, where food is processed, where microbes are in close contact to the host, and where probiotics have a chance to act. Rodent models are not an appropriate surrogate due to coprophagy. Studies that quantify the absolute (not relative) abundances of individual taxa are key to correctly interpreting microbial changes in response to diet, drugs, stress, the environment, etc. In collaboration with Mark Pimentel's lab, Dr. Ismagilov and his lab have performed the largest quantitative study to date of the human small intestinal microbiome. The results reveal a clear relationship between the oral microbiota and the duodenal microbiota. Moreover, this work identified a set of "disruptor" taxa, likely orally derived, that were associated with small intestinal bacterial overgrowth and the prevalence of severe gastrointestinal symptoms. In collaboration with Bana Jabri's lab, Dr. Ismagilov and his lab are using their technologies to analyze small intestinal mucosal biopsies from patients with celiac disease. They are now expanding these studies using a novel approach to shotgun sequencing of mucosa-associated microbial communities to better understand these microbes with strain- and gene-level resolution.

### SESSION 4 BIOGRAPHIES AND ABSTRACTS



### Moderator: Mukesh Verma, Ph.D., National Cancer Institute

Dr. Verma is chief of the Epidemiology and Genomics Research Program's Methods and Technologies Branch at the National Cancer Institute (NCI), National Institutes of Health (NIH). He oversees its research portfolio and initiatives that focus on methods to address epidemiologic data collection, study design and analysis, and modification of technological approaches developed in the context of other research endeavors for use as biomarkers and methods to understand cancer susceptibility. He led the efforts to stimulate and evaluate research in implication of

omics approaches to understand cancer etiology. He represents NCI in NIH Common Fund programs on epigenomics, metabolomics, and molecular transducers of physical activity and a congressionally mandated program on environmental influences on child health outcome. Since joining NCI, he has sought to champion the visibility of and investment in cancer epigenetics research both within the Institute and across other Federal and nongovernmental agencies, and to raise public awareness about controlling cancer. He has received the NCI Director's award five times. Dr. Verma is a member of the editorial boards of *Journal of Personalized Medicine, Journal of Clinical Epigenetics,* and *Technologies in Cancer Research and Treatment*. Dr. Verma holds an M.Sc. from Pantnagar University and a Ph.D. from Banaras Hindu University. He did postdoctoral research at George Washington University and was a faculty member at Georgetown University Medical Center. He has published 187 research articles and reviews and edited 5 books on cancer biomarkers, epigenetics, and epidemiology.



#### Moderator: Terez Shea-Donohue, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases

Dr. Shea-Donohue is a program director in the Division of Digestive Diseases and Nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). She supports basic and translational research related to neurogastroenterology and gastrointestinal (GI) and GI epithelial barrier function. Her research portfolio covers the enteric nervous system including neuroimmune interactions, the brain-gut axis including the impact of neurodegenerative diseases on gastrointestinal physiology, basic and translational

gastrointestinal motility, mechanisms of nonnutrient luminal sensing including those involved in pain, and changes in mucosal barrier function in response to inflammation or infection. She is involved in the NIH Common Fund Program SPARC (Stimulating Peripheral Activity to Relieve Conditions) Component 1 (Anatomical and Functional Mapping), which supports investigations that detail the anatomical and functional mapping of neural circuitry mediating visceral organ pain with the goal of developing device-based therapeutics. Before joining NIDDK, Dr. Shea-Donohue was a professor of medicine at the University of Maryland School of Medicine and at the Uniformed Services University of the Health Sciences.



#### Hyun Jung Kim, Ph.D., University of Texas at Austin

Dr. Kim is an assistant professor in the Department of Biomedical Engineering at the University of Texas at Austin and a principal investigator of the Biomimetic Microengineering (BioME) Laboratory. He has focused on innovating microphysiological platform technologies to uncover fundamental questions in human health and diseases. By leveraging the miniaturized human "guton-a-chip" microsystem, Dr. Kim has created paradigmshifting models that reconstitute the physical structure, physiological function, and mechanical dynamics of the living human intestine (*Nature Protocols, 2022; PNAS, 2016*)

and 2018; iScience, 2019 and 2020). His research group has been particularly interested in emulating a host-microbiome ecosystem that orchestrates human health and diseases by integrating transdisciplinary approaches of clinical microbiology, microfluidics, and tissue engineering. He has spearheaded development of a "patient's avatar" model by integrating patient-derived organoids, fecal microbiota, and tissue-specific immune cells to emulate the pathophysiology of inflammatory bowel disease, including Crohn's disease and ulcerative colitis, and colorectal cancer. He has also disseminated enabling technologies by developing an in vitro three-dimensional morphogenesis-on-a-chip to discover intestinal development, a micro-ecosystem-on-a-chip to coculture obligate anaerobic gut bacteria with host cells, and a leaky gut-on-a-chip to validate health-promoting beneficial functions of probiotic interventions. Dr. Kim has received multiple research funding from the National Cancer Institute's Innovative Molecular Analysis Technologies program, the Helmsley Charitable Trust, the Cancer Research Institute, the Cancer Prevention and Research Institute of Texas, the Kenneth Rainin Foundation, GlaxoSmithKline USA, CJ Cheiljedang, and other nonprofit or for-profit organizations. He has received the Research Excellence in Korean Biomedical Science award, the Technology Impact Award from the Cancer Research Institute, and Innovator Awards from the Kenneth Rainin Foundation.

#### A Pathomimetic Intestinal Disease-on-a-Chip for Validating Microbiome-Based Therapeutics

The drug discovery process has been considerably hampered by the need for animal models that are time- and resource-intensive, ethically questionable, and poor in predicting human drug efficacy and safety. Current in vitro or ex vivo experimental models, including static cell cultures and three-dimensional (3D) organoid cultures, cannot perform a stable long-term coculture with living gut microbiome that has substantially contributed to intestinal homeostasis, metabolism, and immune modulation. Thus, it is a critical unmet

need to develop a human-relevant intestine model that emulates the host-microbiome ecosystem in a mechanically dynamic microenvironment and with an accurate oxygen gradient. Here, Dr. Kim and colleagues discuss a biomimetic human gut-on-a-chip microphysiological system that mimics a 3D lumen-capillary interface under peristalsis-like motions and flow. The intestinal epithelium in a gut-on-a-chip can spontaneously undergo intestinal villus morphogenesis and cellular reprogramming that offers increased mucus production, a tight junction barrier, and drug-metabolizing functions. They showed stable host-microbiome cocultures with probiotic bacteria, infectious pathogens, or an over-thecounter probiotic product from days to weeks. They also demonstrated various microbiomeinduced intestinal pathophysiological milieus such as a "leaky gut" syndrome, pathogenic infection, biofilm formation, and inflammatory immune-microbiome crosstalk. By integrating patient-derived organoids, they can better simulate the pathophysiology of gastrointestinal diseases such as inflammatory bowel disease or colorectal cancer by coculturing patientderived intestinal organoid epithelium and the paired fecal microbiota. They envision that the gut-on-a-chip microsystem will potentially create patient-specific intestinal disease models, dissect the microbial contribution to the disease etiology, and contribute to customized precision medicine.



#### Tom Van de Wiele, Ph.D., Ghent University

Dr. Van de Wiele obtained his Ph.D. degree in applied biological sciences from Ghent University, Belgium in 2004. His postdoctoral research aimed at the study of host-microbe interactions, with particular focus on microbial metabolic potency toward dietary pollutants and plant bioactives. He was a visiting scientist at Ohio State University and worked together with the U.S. Environmental Protection Agency. In 2010, he started the host-microbe interaction technology research unit at Ghent University and in 2015, he received tenure as associate professor at the Center for Microbial Ecology and Technology from

the Faculty of Bioscience Engineering. Through a competitive fast-track procedure from Ghent University he was appointed full professor in 2020. The core expertise of his research group is the creation and application of enabling and validated in vitro technologies that mimic the host-microbe interphase with particular focus on mucosal microenvironments. Model systems such as M-SHIME (a mucosa-containing dynamic gut model) are used to generate mechanistic insight in host-microbe interactions and complement in vivo observations. These platforms also allow the screening of a wide variety of candidate drugs, functional foods, and/or feeds before a narrower selection enters the stage of in vivo trials. Dr. Van de Wiele's research has resulted in a scientific output of more than 250 peer-reviewed international publications of which 9 are highly cited, and yearly participation as invited and keynote speaker at scientific meetings. He was a highly cited researcher in the cross-field discipline in 2021.

#### Personalization of Human Gut Models To Bridge Knowledge Gaps Regarding Interindividual Variability in Efficacy and Mode of Action of Precision Probiotics

The last decade of human microbiome research has increasingly shown its clear association with human health status. The development of in vitro technologies mimicking hostmicrobiome interaction processes in the lab has enabled mechanistic research that complements clinical observations and unravels the putative causal role of the microbiome in health maintenance or disease etiology, progression, and aggravation. This complementary in vitro/in vivo research has also resulted in the development of precision medicine, nutraceuticals, and/or live biotherapeutics as preventive or therapeutic strategies. Yet, a somewhat difficult aspect to grasp is the large degree of interindividual variability in health effects, and intervention studies are often confronted with stratification of the study cohort into responders and nonresponders. This is often related to underlying determinants such as genetic polymorphisms, diet, disease history, and the microbiome. Dr. Van de Wiele will describe how existing in vitro technologies for studying the human gut microbiome can be tailored in experimental setup to better capture this level of interindividual variability and investigate to what extent differences in human microbiome composition or functionality are a contributing factor to the variations in disease severity or therapeutic success. A better understanding of what (microbiome) factors make an individual a responder or nonresponder will also facilitate the development of more personalized medicine and therapies, including the development of precision probiotics.



#### Noah Palm, Ph.D., Yale University

Dr. Palm is an associate professor of immunobiology at Yale University School of Medicine, where his laboratory focuses on understanding how the trillions of microbes that live in and on us (our microbiota) interact with and influence their mammalian hosts. His work particularly emphasizes the development of new technologies to deconvolute complex host-microbiota interactions and reveal causal roles for the microbiota in human health and disease. Dr. Palm received his B.A. in biology from Macalester College and performed doctoral work with Dr. Ruslan Medzhitov and postdoctoral work with Dr. Richard Flavell at Yale University. He is the

recipient of multiple honors and awards, including the Smith Family Foundation Award for Excellence in Biomedical Research, Pew Biomedical Scholar Award, and National Institutes of Health Director's New Innovator Award.

#### Mapping Uncharted Landscapes of Host-Microbiota Connectivity

The myriad bacteria that live in and on us have diverse impacts on human physiology, yet the molecular details underlying host-microbiota interactions remain largely unknown. To map the host-microbiota interactome, Dr. Palm and his team developed a novel technology, called BASEHIT, that enables comprehensive evaluation of interactions between individual bacterial strains and thousands of human extracellular proteins. Using BASEHIT, they evaluated over 1.6 million potential interactions between 518 phylogenetically and functionally diverse human-associated bacterial strains and 3,143 human extracellular

proteins. The resulting host-microbiota interactome atlas contains hundreds of previously undiscovered interactions that may contribute to tissue colonization, immunomodulation, and strain-specific impacts on human disease. By dramatically expanding the landscape of known host-microbiota interactions, these studies will facilitate molecular dissection of the microbiota's influence on human biology.



#### Emily P. Balskus, Ph.D., Harvard University

Dr. Balskus graduated from Williams College in 2002. She then spent a year at the University of Cambridge as a Churchill Scholar in Professor Steven Ley's lab. She received her Ph.D. from the Department of Chemistry and Chemical Biology (CCB) at Harvard University in 2008; her graduate work with Professor Eric Jacobsen focused on the development of asymmetric catalytic transformations and their application in total synthesis. From 2008 to 2011 she was a National Institutes of Health postdoctoral fellow at Harvard Medical School in Professor Christopher T. Walsh's lab, where her research involved elucidating and

characterizing biosynthetic pathways for the production of small molecule sunscreens by photosynthetic bacteria. Dr. Balskus joined the CCB faculty in 2011 and is currently a professor of chemistry and chemical biology and an investigator of the Howard Hughes Medical Institute. She is also an institute member of the Broad Institute of MIT and Harvard, a faculty associate of the Microbial Sciences Initiative at Harvard, a member of the Harvard Digestive Diseases Center, and a member of the MIT Center for Microbiome Informatics and Therapeutics. Her independent research focuses on discovering and characterizing microbial metabolic pathways and enzymes, with an emphasis on activities from the human gut and vaginal microbiomes. Her group's work has been recognized with multiple awards, including the 2013 Packard Fellowship for Science and Engineering and the 2020 Alan T. Waterman Award from the National Science Foundation.

#### Deciphering the Human Microbiome With Chemistry

The human body is colonized by trillions of microorganisms that exert a profound influence on human biology, in part by providing functional capabilities that extend beyond those of host cells. The microbiota can both synthesize unique metabolites and transform ingested compounds and host-derived molecules, and this metabolism may influence host biology in positive and negative ways. However, we still do not understand the vast majority of the molecular mechanisms underlying gut microbial metabolism. Major obstacles faced in surmounting this knowledge gap include the difficulty linking functions associated with the human gut microbiota to specific microbial enzymes and the challenge of controlling these activities in complex microbial communities. In this talk, Dr. Balskus will discuss approaches for discovering and characterizing gut microbial enzymes and metabolic activities. Gaining a molecular understanding of these activities will not only help to elucidate mechanisms underlying microbiota-host interactions but may also guide the selection and development of probiotic bacteria.



#### Curtis Huttenhower, Ph.D., Harvard University

Dr. Huttenhower is a professor of computational biology and bioinformatics in the Departments of Biostatistics and Immunology and Infectious Diseases at the Harvard T.H. Chan School of Public Health, where he codirects the Harvard Chan Microbiome in Public Health Center. He is an associate member of the Broad Institute's microbiome program. His lab focuses on computational methods for functional analysis of microbial communities and molecular epidemiology of the human microbiome. This includes systems biology reconstructions integrating metagenomic, metatranscriptomic, and other microbial community omics;

the microbiome in health and disease; and its potential as a diagnostic tool and point of therapeutic intervention.

#### Probiotic Bioactivity in the Human Microbiome

While "probiotics" can be used to refer to diverse products, they ultimately all include live microbes that have some nominally beneficial effect on human health. The mechanisms of such effects can be diverse: live microbes can engraft in an environment like the gut, or they can pass through transiently; they can produce helpful (or harmful) small molecule metabolites; these metabolites can have local or systemic effects; microbial protein products can change host-microbe or microbe-microbe interactions; or immune components can respond to individual microbes or to overall ecological shifts. The Human Microbiome Bioactives Resource (HMBR) provides a set of resources for discovery, validation, and early-stage translation of such diverse types of bioactivity, which can be applied to infer mechanisms that may be causal in probiotic effects. Dr. Huttenhower will discuss resources from the HMBR for bioactive discovery in inflammatory bowel disease (IBD), including a meta-analysis of over 5,000 IBD gut microbiomes, bioinformatic tools for prioritizing candidate leads, and in vivo validation of microbial polyamine products, pilin variants, and von Willebrand factor homologs. Dr. Huttenhower will also discuss how these techniques can be applied to better understand the effects of "traditional" dietary probiotics and "next generation" engineered probiotics in human populations as well as some common pitfalls, gaps, and next steps in their development.



### Barbara Rehermann, M.D., National Institute of Diabetes and Digestive and Kidney Diseases

Dr. Rehermann is chief of the Immunology Section, Liver Diseases Branch, at the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health (NIH) in Bethesda, Maryland. She received an M.D. degree and the Venia Legendi for Immunology from Medizinische Hochschule, Hannover, Germany. She completed a clinical residency and fellowship in the Department of Gastroenterology, Hepatology, and Endocrinology at the same university (1991–1993) and a postdoctoral research fellowship at the Scripps Research Institute, La Jolla, California (1993–1995). Her scientific interests include innate and adaptive immunology, the gut-liver axis, and the microbiome. By learning from naturally coevolved microbiota, she is aiming to increase the translational research value of the laboratory mouse. She is an elected member of the American Society for Clinical Investigation, the American Academy of Microbiology, and the German National Academy of Sciences Leopoldina and a fellow of the American Association for the Study of Liver Diseases. Dr. Rehermann's publications have been cited over 13,000 times. She has trained more than 55 postdoctoral fellows and students, many of whom now hold academic positions in the United States, Germany, Italy, South Korea, and Japan.

#### Wild Mouse Microbiota and Pathogens in Preclinical Research Models

Laboratory mice are paramount for understanding basic biological phenomena but also have limitations in preclinical studies. Based on the concept that natural microbiota coevolved with their respective hosts under evolutionary pressure of common environmental immune stimuli, Dr. Rehermann will describe mouse models, developed in her laboratory at NIH, that combine the natural microbiota and pathogens with the tractable genetics of laboratory mice. Wild mouse microbiota are stable over multiple generations of laboratory mouse colonies. The presence of wild mouse microbiota and pathogens improves the utility of the mouse as a preclinical model in predicting innate and adaptive immune responses of humans.



#### Sameer Sonkusale, Ph.D., Tufts University

Dr. Sonkusale is currently a professor of electrical and computer engineering at Tufts University, with a joint appointment in the Department of Biomedical Engineering and the Department of Chemical and Biological Engineering. He also held a visiting appointment at the Wyss Institute at Harvard University and at Brigham and Women's Hospital of Harvard Medical School for 2011–2012 and 2018–2019. Dr. Sonkusale is a past associate dean of graduate education in the School of Engineering at Tufts University. Currently, he directs an interdisciplinary research group nano lab with a research focus on biomedical micro devices circuits

and systems, flexible bioelectronics, point-of-care diagnostics, precision medicine, and miniaturized bioinstrumentation. Dr. Sonkusale received his M.S. and Ph.D. degrees in electrical engineering from the University of Pennsylvania. He has received several awards, including the National Science Foundation CAREER Award in 2010. Dr. Sonkusale is on the editorial boards of *Scientific Reports* (Nature Publishing Group), *IEEE Transactions on Biomedical Circuits and Systems, Journal of Low Power Electronics and Application, Chips, PLoS One,* and *Electronic Letters*.

#### Lab-on-a-Pill for Spatially Targeted Sampling of Gut Microbiome

This talk will cover emerging ingestible technologies for *spatial sampling* of the gut microbiome. This technology is designed to meet the need for sampling the gut lumen in situ and noninvasively to improve our understanding of the microbiota's role in health and

disease. Most studies infer the condition of the gut microbiome from the analysis of fecal DNA and other molecules. Because the gut environment changes as the gut content moves down the gastrointestinal (GI) tract, analyses of feces are inadequate to identify abnormal conditions upstream of the distal colon. This lab-on-a-pill technology will eliminate a major limitation of analytical approaches based on the examination of feces. A capsule capable of sampling the lumen of specific GI organs will broadly benefit research on different GI conditions associated with dysbiotic microbial communities, ranging from enteric infections with opportunistic pathogens to age-related chronic conditions and to inflammation. It has the potential to address the challenges related to poor replicability or clinical translation of probiotics research by providing a gold standard for ensuring rigor and replicability through the analysis of spatial distribution of microbiome in the GI tract.

### PLANNING COMMITTEE

#### Joseph M. Betz, Ph.D., Office of Dietary Supplements (see biography on page 26)



### Wen Chen, Ph.D., National Center for Complementary and Integrative Health

Dr. Chen is chief of the Basic and Mechanistic Research Branch in the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH), National Institutes of Health. The branch supports research using a variety of approaches, ranging from biochemical, cellular, physiological, and imaging to behavioral methods, to investigate the basic science and mechanistic processes of complementary and integrative health in biological systems including cells, tissues and organs, animal models, and humans. Dr. Chen holds a Ph.D.

in biological chemistry and molecular pharmacology from Harvard University. Under the tutelage of Dr. Michael E. Greenberg at Harvard Medical School, she studied the epigenetic regulation of activity-dependent expression of brain-derived neurotrophic factor (BDNF). She also earned a master's degree in medical sciences as part of the Harvard-Markey Medical Scientist training program at Harvard Medical School. Dr. Chen did her postdoctoral training in proteomics at Massachusetts Institute of Technology. Prior to joining NCCIH, Dr. Chen worked as a scientific editor at *NEURON*, a program coordinator at the National Institute of Mental Health, and a program director at the National Institute on Aging. She has published on transcriptional and epigenetic regulation of BDNF, aging and central neural control of mobility in older adults, pharmacological management of chronic pain, harnessing neuroplasticity for clinical applications, chemical senses and aging, and proteomics.



#### Cindy D. Davis, Ph.D., U.S. Department of Agriculture Agricultural Research Service

Dr. Davis serves as national program leader for the program in human nutrition conducted by the U.S. Department of Agriculture (USDA) Agricultural Research Service. In this role, she helps direct the scientific program for six Human Nutrition Research Centers. Prior to joining USDA, she was the director of grants and extramural activities in the National Institutes of Health (NIH) Office of Dietary Supplements (ODS), where she actively engaged and encouraged partnerships with NIH Institutes and Centers to develop a portfolio that advances both nutritional and

botanical dietary supplement research for optimizing public health. She is also actively involved in a number of Government working groups focused on the microbiome, including

being cofounder and cochair of the Joint Agency Microbiome Working Group. Before coming to ODS, she was a program director in the Nutritional Sciences Research Group at the National Cancer Institute. Dr. Davis received her bachelor's degree with honors in nutritional sciences from Cornell University and her doctorate degree in nutrition with a minor in human cancer biology from the University of Wisconsin–Madison. She completed her postdoctoral training at the Laboratory of Experimental Carcinogenesis at the National Cancer Institute. She then joined the Grand Forks Human Nutrition Research Center, USDA, as a research nutritionist. In 2000, she received a Presidential Early Career Award for Scientists and Engineers and was named a USDA Early Career Scientist. She is a supplement editor for the *Journal of Nutrition* and assistant editor for *Nutrition Reviews*.



### Roberto Flores, Ph.D., M.S., M.P.H., Office of Nutrition Research

Dr. Flores serves as a coordinator for the National Institutes of Health (NIH)-wide Nutrition Research Implementation Working Groups (IWGs) in the Office of Nutrition Research (ONR) at NIH. In this role, he facilitates the implementation efforts for the 2020–2030 Strategic Plan for NIH Nutrition Research and supports the activities of the IWGs with ONR and NIH Institutes, Centers, and Offices. Dr. Flores also serves as cochair for the Microbiome, Diet, and Health Interrelationships Implementation Work Group. Prior to joining ONR, Dr. Flores served as program director for

the Nutritional Science Research Group, Division of Cancer Prevention, at the National Cancer Institute (NCI) from 2013 to 2020. Dr. Flores earned his M.S. and Ph.D. in nutritional sciences, with an emphasis on nutritional biochemistry and cancer biology, from the University of Arizona. He also holds a master's degree in public health with a focus on epidemiology, vaccine science, and policy from the Johns Hopkins School of Public Health. His areas of expertise are human microbiome and nutrition research (pre- and probiotics, diet-microbiome-health interrelationships); mechanisms of obesity and cancer; infectious disease epidemiology (human papillomavirus [HPV] and cervical cancer, HPV infection in men); bioassay development and validation (quality assurance/quality control methods and performance assessment); molecular screening of viral infections; next generation sequencing technologies in cancer research and infectious disease; cancer prevention and control programs; grant management; and scientific program coordination and development.

Frank A. Hamilton, M.D., M.P.H., M.A.C.G., A.G.A.F., National Institute of Diabetes and Digestive and Kidney Diseases (see biography on page 16)



#### David A. Jett, Ph.D., National Institute of Neurological Disorders and Stroke

Dr. Jett is a program director at the National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), where he leads the Office of Neural Exposome and Toxicology and the NIH Countermeasures Against Chemical Threats (CounterACT) Program. He also serves as the scientific team leader within the Division of Translational Research and leads several new initiatives including the influence of the microbiome on dementia and pain. After receiving a Ph.D. in neurotoxicology at the University of Maryland School of Medicine, Dr. Jett

conducted postdoctoral research and subsequently joined the faculty at Johns Hopkins University's Bloomberg School of Public Health. Dr. Jett's scientific interest is in the impact of chemical agents and exposomic factors on nervous system function across the lifespan. Dr. Jett has authored many scientific articles and book chapters in neurotoxicology and has chaired sessions and given keynote addresses at many national and international scientific meetings. He holds the position of Professor Adjunct of Chronic Disease and Epidemiology within the Yale School of Public Health. Dr. Jett has served on White House and intergovernmental committees that set the nation's research priorities, as well as science advisory panels for the Environmental Protection Agency and the Department of Defense. Dr. Jett's other major interest at NIH is training and programs designed to increase diversity in the neuroscience research workforce.



#### Hye-Sook Kim, Ph.D., National Center for Complementary and Integrative Health

Hye-Sook Kim, Ph.D., is a program director in the Basic and Mechanistic Research (BMR) Branch of the Division of Extramural Research at the National Center for Complementary Health (NCCIH) at the National Institutes of Health (NIH). She maintains a portfolio focused on fundamental mechanistic research underlying the effects of prebiotics, probiotics, and microbiome-/microbial-based treatments. Dr. Kim came to NCCIH after a brief stint as a senior R&D manager in the Institute of Advanced Technology at CJ-Cheil Jedang Corporation (CJ Corp.) in South Korea.

There she oversaw a biopharma research group to develop microbiome-based therapeutics for treating neurological disorders, immune-related diseases, and cancer. Prior to CJ Corp., she was a project leader at the Delaware-based DuPont, where she managed human gut microbiome and probiotic projects aimed at ameliorating metabolic disorders and improving gastrointestinal health. Dr. Kim's areas of expertise include bacteriology, molecular biology, biochemistry, bioinformatics, and host-microbe interactions. Dr. Kim earned her Ph.D. in plant pathology from the University of Wisconsin-Madison. She did her postdoctoral training in the Department of Biochemistry and Molecular Biology at the University of Chicago, where she studied the regulatory mechanisms of a BSL-3 bacterial pathogen during host adaptation.



### Li Lin, Ph.D., National Institute on Alcohol Abuse and Alcoholism

Dr. Lin joined the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health after a research career at Johns Hopkins University and the National Institute on Aging, where her work focused on immunobiology, vascular inflammation, and receptor biochemistry and signaling. She also has experience in protein engineering and transgenic animal models for aging research. Her portfolio covers broad research interests including immunobiology (innate and adaptive immunity), lung and mucosal pathology, inflammation, vascular biology,

biology of aging, and proteostasis. Dr. Lin obtained her Ph.D. in biochemistry and molecular biology from the State University of New York at Stony Brook (currently Stony Brook University) and completed postdoctoral training in immunobiology at Yale University and the Gladstone Institute of Virology and Immunology at the University of California, San Francisco.

**R. Dwayne Lunsford, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases** (see biography on page 9)

Padma Maruvada, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases (see biography on page 28)



#### Young Oh, Ph.D., National Heart, Lung, and Blood Institute

Dr. Oh is deputy branch chief of the Vascular Biology and Hypertension Branch in the Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH). Dr. Oh received his B.S. from Chung-Ang University, Seoul, Korea; M.S. from the California State University, East Bay; and Ph.D. in physiology and biophysics from the University of Alabama at Birmingham (UAB) in 1992, working on biochemical and molecular characterization of epithelial sodium channels in the kidney. He then finished his postdoctoral training at

Yale University, working on molecular biology of voltage-gated ion channels. Dr. Oh was then recruited as an assistant professor of medicine in the Division of Nephrology at UAB, where he worked on ion channel gene mutations associated with human hypertension. During this time, he held a joint appointment in the Department of Neurobiology, working on glial cell biology. Dr. Oh joined the NIH intramural research program in 2002. He has a long relationship with NIH as grantee, grant reviewer, intramural scientist, and extramural scientist. He currently manages a grant portfolio related to hypertension and vascular biology research.

Ryan Ranallo, Ph.D., National Institute of Allergy and Infectious Diseases (see biography on page 28)

Gabriela Riscuta, M.D., M.S., C.N.S., National Cancer Institute (see biography on page 9)

Terez Shea-Donohue, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases (see biography on page 34)



Barbara C. Sorkin, Ph.D., M.S., Office of Dietary Supplements

Dr. Sorkin received her B.S. and M.S. from the Department of Molecular Biophysics and Biochemistry at Yale University and her Ph.D. from the Laboratory of Developmental and Molecular Biology at Rockefeller University. She was a faculty member at the Scripps and Forsyth Research Institutes and currently codirects the National Institutes of Health (NIH) Consortium for Advancing Research on Botanical and Other Natural Products (CARBON) from the NIH Office of Dietary Supplements (ODS). CARBON is a collaborative research centers program focused

on advancing understanding of the chemistry and biological activities of botanicals and other natural products relevant to dietary supplements. Dr. Sorkin administered a research portfolio including healthy aging, cancer, and sleep at the NIH National Center for Complementary and Alternative Medicine (NCCAM; now the National Center for Complementary and Integrative Health) for 9 years before moving to ODS. While at NCCAM she also coordinated programs to enhance clinical and translational research on complementary and alternative medicine.

Ashley Vargas, Ph.D., M.P.H., R.D.N., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (see biography on page 16)

Mukesh Verma, Ph.D., National Cancer Institute (see biography on page 34)



#### Jean Yuan, M.D., Ph.D., National Institute on Aging

Dr. Yuan is the program director for translational bioinformatics and therapeutics development at the National Institute on Aging (NIA), National Institutes of Health (NIH). She completed training in clinical medicine, computer science, and bioinformatics. Prior to joining NIA, Dr. Yuan served as the scientific review officer managing NIH applications in the areas of biomedical computing, health informatics, mobile health technology/smart devices, and Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) health informatics. Dr. Yuan has broad expertise in data science and preclinical

and clinical drug development, as exemplified in the development of NIH portfolio analysis tools (iSearch/iPatent tool). She was the project lead of pharmacogenomics and precision medicine programs across multiple disease areas at a pharmaceutical company prior to joining NIH.