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Editorial overview: Frontiers in microbiome studies: viewing vast vistas with roadmap in hand

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Karen Guillemin is the founding director of the META Center for Host-Microbe Systems Biology at the University of Oregon, devoted to investigating host-microbiota systems dynamics and functions. Her group pioneered the gnotobiotic zebrafish model to study microbiota assembly and the impacts of microbiota on tissue development and homeostasis.

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Julie Segre is a Senior Investigator at the National Human Genome Research Institute, NIH. Segre's research defined the human skin-associated bacterial, fungal and viral communities, enabling studies of pediatric atopic dermatitis, primary immunodeficiency and emerging pathogens. Segre's research also integrated whole genome sequencing of hospital pathogens to study nosocomial transmission.

This series explores frontiers of microbiota research, with articles focused on understanding host-associated microbial composition, dynamics and function. We invited experts in the field to write about a wide set of ecological and evolutionary forces and molecular mechanisms that shape microbial communities. Over the past couple of decades, our knowledge of host-microbiome interactions has been expanded by the revolution in genomic sequencing that enabled a broader appreciation of the composition of microbial communities. The articles in this volume illustrate our expanding conceptualization of host-associated microbiota, moving beyond characterizations of communities from single individual hosts to consider microbiota of host populations, considering microbiota composition across different time scales, and expanding community characterizations beyond bacteria to all microbial life forms. This series also provides well thought-out roadmaps for inferring microbiota functions through the application of conceptual frameworks and the use of reductionist, simplified and genetically tractable microbial systems to yield functional, mechanistic insights.

Robinson, Bohannan, and Britton explore the importance of inter-host transmission in shaping microbiota compositions. They consider how studies of microbiomes at the level of host populations will require new types of data collection and integration, for example tracking social networks. They propose that tractable animal model systems will be critical for establishing new paradigms for studying microbiota transmission.

Exploring another expanding dimension of microbiota, Schlomann and Parthasarathy discuss community dynamics and consider the temporal scales across which these communities change. They note both the capacity for relative community stability over long, multigenerational times scales, and the possibility for rapid and dramatic fluctuations of communities. Understanding these dynamics across different timescales, they argue, is essential for predictive models of microbiota responses to perturbations.

Porras and Brito consider the global context in which we describe microbial communities as a future frontier of microbiota research. They describe vast differences in microbial composition across global human populations. This microbial diversity serves as an enormous reservoir of opportunity to identify new microbial products with functions in pathogen colonization resistance. Natural probiotic strains may be the key to improving outcomes for perinatal sepsis or severe acute malnutrition. However, these inherent microbial community differences may also affect the efficacy of novel therapeutic modalities such as topical HIV prophylaxis. They consider the challenges

and opportunities for promoting inclusivity within human microbiome research.

Kuthyar, Manus, and Amato explore the topic of microbiota transmission in their survey of nonhuman primates microbiota studies. Because nonhuman primates are so well characterized for their diversity of social structures, these organisms provide exceptionally powerful models for comparative studies of the microbiota transmission as a function of social interactions.

Another powerful model system for social microbiota studies, the honeybee, is presented by Miller, Parish, Newton. These authors describe the observational and manipulative studies that have been performed with these model eusocial insects, in which strict caste and life stages roles alter host physiology and determine the extent to which individuals interact with different source pools of microbes in the hive and in the environment.

Bongrand and Ruby present recent data on bacterial strain epidemiology in the classic symbiosis model system, the Hawaiian bobtail squid and its luminescent symbiont, *Vibrio fischeri*. They describe new insights into the strain level competition dynamics that play out during establishment of the symbiosis and may serve as a model of similar strain-level dynamics in more complex microbiota.

Reese and Kearney provide an evolutionarily-informed model of microbial and host functional trade-offs that shape these intimately inter-dependent interactions. First, they provide a framework to understand how animals aim to optimize their growth and reproductive success under environmental constraints. Next, they transition to discuss how gut microbiota, which play roles in metabolism, immunity, behavior, and other diverse physiological traits, are an integral part of animal biology, subject to trade-offs experienced at the host and the microbial level. Finally, they present dietary intervention as a case study where both microbial and host trade-offs are likely to be relevant and evolutionarily linked. They discuss implications for human health and how to design future work on the microbiota considering trade-offs within an evolutionary framework.

Cosetta and Wolfe combine microbial ecology and systems biology to explore broader biological scales of multispecies interactions that shape the diversity of microbial communities. They highlight challenges and opportunities in the study of microbial interactions that span from the cellular to the species to the community scale focused on interactions in relatively simple fermented food. They explore bacterial–fungal interactions in microbiota and the evolutionary forces that establish and maintain these complex relationships.

In their review, Stubbendieck, Li, and Currie use three different bipartite symbioses of the Hawaiian bobtail squid, the leguminous plants, and the fungus farming ants, as a framework to consider how specialized host morphological structures enable receptions of particular bacterial chemical signals important to the biology of these systems. They suggest that similar signal-structure interfaces may play important roles in more complex host-microbial systems.

In their review of the impact of the mammalian gut microbiota on cardiovascular diseases, Kasahara and Rey lay out a comprehensive experimental pipeline for moving from associations between microbiota and disease phenotypes to causative relationships. They illustrate how gnotobiotic mouse models, combined with collections of genetically tractable microbes, can be deployed to establish how specific microbial metabolites impact host health. With this knowledge in hand, they demonstrate how particular dietary interventions can be used to manipulate microbiota composition and metabolite production for therapeutic purposes.

Fiers, Gao and Iliev explore the recent explosion in interest (finally) in the human fungal 'mycobiota' that has now been linked to diverse disorders such as colitis and pancreatic cancer progression. Recent advances in culturing and sequencing have begun to reveal a diverse mycobiome that interacts directly with both host immune cells and with the bacterial microbiota. They discuss future challenges for exploring symbiotic and pathogenic fungi in human health over a lifespan.

Finally, Whitfill and Oh discuss opportunities and limitations in microbiome engineering, focusing on a new generation of tools for *in situ* genetic modification of microbiomes. Targeted genetic engineering and synthetic biology have generated new modes for engineering the microbiome, including targeting select microbes, precise spatial and temporal gene expression, and living biosensors. Whitfill and Oh's review conceptualizes how precision modification of the microbiome will yield functional information essential to develop new therapeutic modalities predicated on microbial communities.

Collectively, these articles demonstrate the scope and promise of microbiota studies. We are awed by how much there is to learn about host-associated microbial communities across diverse host populations along different spatial, temporal, and phylogenetic scales. Simultaneously, we are emboldened by the elegant and creative approaches our colleagues are pursuing to understand the principles by which host-associated microbiota assemble and function.