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A unified initiative to harness Earth's microbiomes:

Transition from description to causality and engineering

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Policy Forum

Despite their centrality to life on Earth, we know little about how microbes (1) interact with each other, their hosts, or their environment. Although DNA sequencing technologies have enabled a new view of the ubiquity and diversity of microorganisms, this has mainly yielded snapshots that shed limited light on microbial functions or community dynamics. Given that nearly every habitat and organism hosts a diverse constellation of microorganisms—its "microbiome"—such knowledge could transform our understanding of the world and launch innovations in agriculture, energy, health, the environment, and more (see the photo). We propose an interdisciplinary Unified Microbiome Initiative (UMI) to discover and advance tools to understand and harness the capabilities of Earth's microbial ecosystems. The impacts of oceans and soil microbes on atmospheric CO2 are critical for understanding climate change (2). By manipulating interactions at the root-soil-microbe interface, we may reduce agricultural pesticide, fertilizer, and water use enrich marginal land and rehabilitate degraded soils. Microbes can degrade plant cell walls (for biofuels), and synthesize myriad small molecules for new bioproducts, including antibiotics (3). Restoring normal human microbial ecosystems can save lives [e.g., fecal microbiome transplantation for Clostridium difficile infections (4)]. Rational management of microbial communities in and around us has implications for asthma, diabetes, obesity, infectious diseases, psychiatric illnesses, and other afflictions (5, 6). The human microbiome is a target and a source for new drugs (7) and an essential tool for precision medicine (8).

The National Science Foundation's Microbial Observatories, the U.S. Department of Energy's Genomic Sciences program, the National Institutes of Health's Human Microbiome Project, and other efforts in the United States and abroad have served as critical first steps in revealing the diversity of microbes and their communities. However, we lack many tools required to advance beyond descriptive approaches to studies that enable a mechanistic, predictive, and actionable understanding of global microbiome processes. Developing these tools requires new

collaborations between physical, life, and biomedical sciences; engineering; and other disciplines.

AREAS OF EMPHASIS.

A central purpose of the UMI is to develop cross-cutting platform technologies to accelerate basic discovery and translation to applications. We highlight key needs and opportunities.

***Decrypting microbial genes and chemistries*.**

Approaches for characterizing microbiomes increasingly rely on whole-community metagenomic sequencing, yet roughly half of the genes identified in these studies encode products of unknown function, and existing functional annotations are often incomplete or inaccurate (9). Technologies for resolving roles of uncharacterized genes with high throughput and high accuracy are needed. These approaches must integrate improved computational methods for in silico prediction of protein and RNA functions, rapid mutagenesis of model organisms or native strains under natural conditions, multi-omics and high-resolution phenotyping platforms to test functional predictions in vitro and in situ, and improved capture of information in the literature.

Deciphering chemistries of microbiomes is essential. In untargeted metabolomics studies using mass spectrometry, less than 2% of data can be matched to known chemical compounds, and only a fraction of those map to recognized biochemical pathways (10). Advances have been made in predicting structures from mass spectra, but improvements are needed in both in silico and physical technologies to illuminate the “dark matter” of microbial chemistries.

Cellular genomics and genome dynamics.

Simply knowing which genes are present in a microbial population, without understanding their physical linkage, precludes organism-based insights into community function and dynamics. A transition from gene-centric to whole-genome– based analyses is vital and will require technologies capable of generating complete and assembled genomes from individual cells in complex microbiomes with high throughput, low cost, and minimal quantities of DNA. Advances are needed in long-read and single-cell sequencing platforms, improved algorithms for genome assembly, and comprehensive collections of reference genomes.

High-throughput, high-sensitivity multi-omics and visualization.

Studies that integrate metagenomics, transcriptomics, proteomics, and metabolomics have been reported, but they are limited by coarse temporal and spatial scales and the absence of contextual information. Future discoveries will require new multimodal imaging capabilities that allow individual microbes—and their interactions, products, and identities—to be visualized

within complex communities (11). Techniques that integrate high-resolution optical imaging with submicron-scale spectroscopy, and nondestructive nanoscale sensing platforms that allow longitudinal measurements, will help us understand how chemical conversations shape microbial communities and their environments.

Modeling and informatics.

Comprehensive understanding of a microbial community can only be achieved by integrating imaging and multi-omics data sets with measurements of environmental or host parameters over relevant temporal and spatial scales. Adaptive models that capture the complexity of interactions from molecules to microbes, and communities to ecosystems, and new approaches for visualizing complex data sets in multiple dimensions, will contribute to a systems biology of microbiomes capable of yielding models with high predictive value. This will require new computational tools and innovations in mathematics, statistics, machine learning, and related fields. To ensure that data are openly available in a common format that can be processed by diverse computational tools, data commons, and standard languages for data reporting, such as those developed by the Genomic Standards Consortium (12), will be essential.

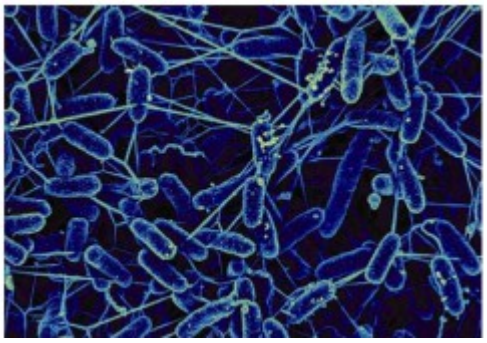
Perturbing communities in situ and tractable model systems.

Transitioning microbiome research from a correlative science to one based on experimental assessments of causality requires tools for manipulating microbial communities. Precision approaches are needed for stimulating, inhibiting, adding, removing, or altering microbes and their genes in situ, alone, or in combination and without cultivation. Potential tools include sequence-specific gene editing using CRISPR/Cas9 delivered by phage or conjugative elements (13), contractile nanotubes with strain-specific bactericidal activity (14), defined nutrient combinations based on modeled metabolic networks, and synthetic microbial consortia engineered to disrupt or replace existing communities. Tractable model systems that approximate natural environments, including culture-based methods, and studies of naturally occurring microbiomes of low complexity such as those found in several insects, squid, and other organisms, will enable discoveries of mechanisms that drive interactions between microbes and their habitats (15).

IMPLEMENTATION.

These goals are ambitious, but not beyond reach. Many tools we call for are extensions of existing technologies, albeit ones that will require ingenuity and resources to implement. Over the near term of 5 years, these tools could reorient the field from correlative studies to hypothesis-driven approaches capable of establishing precise causal relationships. Over a longer term of 10 years, we envision a leap toward predictive understanding that allows evidence-based, model-informed microbiome management and design.

Realizing the goals of the UMI will require a continuing and well-resourced public-private effort. Involving physical scientists, engineers, and others in an interdisciplinary initiative will lead to tool development and insights that have applications in different environments and beyond microbiome research. This creates the potential to accelerate and transform research supported by multiple government agencies, private foundations, and industries, with anticipated economies of scale. Alignment of efforts of the many funders of microbiome-related research could leverage existing resources for greater yield, forge new funding approaches, amplify benefits of increased investment, and attract entities not yet involved in microbiome-related research.



Microbial community. *Shewanella oneidensis* with electron-conducting protein nanowires form an electric circuit to respire by transferring electrons to metal oxide.

Funding mechanisms will need to reflect the crosscutting nature of the initiative. In addition to traditional agency-specific requests for proposals, multi-agency joint calls for development of broadly applicable tools could ensure coordination and availability of sufficient resources while reducing redundancy. These mechanisms should be designed to attract, train, and support diverse, multidisciplinary networks of scientists and engineers and to encourage disruptive ideas. Efforts should be made to identify microbiome-related translational opportunities and reduce barriers to industry participation.

The research community must help steer this effort by participating in the exchange between disciplines and by communicating insights and implications. The scientific community must also integrate ethicists, social scientists, regulators, and legal professionals at an early stage to ensure that risks associated with microbiome research are accurately assessed and proactively addressed.

As U.S. scientists, we call for a national initiative, but the challenge warrants a concerted global response to promote good practice and speed progress. Such an alliance could develop large-scale international collaborations and coordinate shared assets and consensus standards for

global microbiome research. Fueled by the energy and vision of the scientific community and cross-cutting public and private partnerships, the UMI will lead to scientific insights, technological advances, and economic opportunities of lasting benefit to future generations.

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SUPPLEMENTARY MATERIALS

Supplementary Text

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