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Engineering Microbiomes—Looking Ahead

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Microbiomes, the collective of microbes within a community, shape the natural world. They exist in, on, and around nearly every organism and environment on Earth. Microbiomes interact with their environments in key ways, forming dynamic relationships and interactions with biotic and abiotic elements of their environments. Over the past 20 years, advances in sequencing and -omics technologies have helped transform microbiome research from limited snapshots of microbial community composition to reveal vibrant, dynamic panoramas of microbiomes and their interactions. Now, new tools to manipulate and grow communities in the lab, perform large-scale, high-throughput experiments, and better understand the roles of different constituent community members, make the prospect of *engineering* microbiomes a challenging but achievable goal for the next 20 years.

The engineering of microbiomes could facilitate revolutionary changes in food production, human and animal health, and environmental preservation and restoration. Engineered microbiomes could reduce or eliminate the need for environmentally damaging fertilizers, while facilitating increased disease resistance in staple crops. Personalized human microbiomes may help prevent diseases or even enhance human health. Ocean microbiomes can be engineered to reduce and mitigate plastic and microplastics pollution. Together, these and many other applications of engineered microbiomes hold the potential to transform our world.

To help achieve the future we envision, we published a technical research roadmap entitled *Microbiome Engineering: A Research Roadmap for the Next-Generation Bioeconomy*,[1] examining the current state and technical hurdles of microbiome engineering research, outlining future advances that will be needed to continue driving the field forward, and considering the regulatory and social changes that will be needed so these technologies can be deployed in a manner that is safe for people and the environment. The roadmap is the result of a collaborative effort involving over 40 faculty members, industry experts, postdoctoral fellows, and graduate students, and aims to be a resource for both the research community and policymakers interested in advancing the field of microbiome engineering.

Microbiome Engineering examines the major scientific and engineering breakthroughs that will be needed to engineer microbiomes and details specific milestones to benchmark progress toward that breakthrough. Community discussions about the future of microbiome engineering research resolved into three main technical themes of the roadmap: *Spatiotemporal Control*, *Functional Biodiversity*, and *Distributed Metabolism* (Figure 1). *Spatiotemporal Control* considers how the position and function of microbes within a microbiome can be engineered precisely and predictably, both in space and over time. *Functional Biodiversity* discusses how to engineer functionally similar, but taxonomically diverse, collections of organisms in a microbiome, to maintain stable function across environments. Looking forward, we believe that engineering diversity is of particular importance because it will be critical for applications involving microbiomes outside of the lab, but

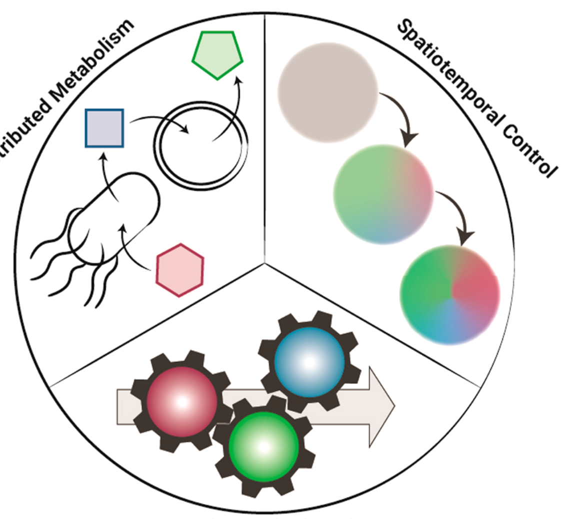

Figure 1. Microbiome Engineering Technical Themes. The roadmap considers three areas for technical advancements in microbiome engineering over the next 20 years. Together these themes encompass milestones toward the achievement of tools and technologies for microbiome engineering across myriad contexts and application spaces. Figure reproduced with permission from ref 1. Copyright 2020 Engineering Biology Research Consortium.

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is potentially one of the least-developed areas of microbiome research. *Distributed Metabolism* focuses on designing microbiomes that leverage the unique metabolic capabilities of individual microbial species to cooperate in their intended *in situ*, engineered function.

The roadmap also explores how engineered microbiomes can be applied in novel ways to help solve societal challenges. While human health and nutrition may be improved via engineering of the human gut microbiome,[2,3] compelling opportunities are emerging across many disciplines. More efficient food production to feed a growing population with less fertilizers are achievable by engineering soil microbiomes. Similarly, we could "make microbes the meal", tailoring the community composition for optimal nutrition making microbiomes a source of alternative food proteins. The societal challenges are derived from our 2019 roadmap *Engineering Biology*[4] and are divided into five Application Sectors: Industrial Biotechnology, Health and Medicine, Food and Agriculture, Environmental Biotechnology, and Energy. The microbiome engineering objectives in these five application spaces, and the technical achievements that accompany the objectives, demonstrate the broad future impact associated with microbiome engineering toward overcoming these societal challenges.

To illustrate one focus area of the roadmap, the technical theme *Distributed Metabolism* examines one of the most exciting elements of microbiome engineering. Metabolic engineering research has allowed many new chemicals to be synthesized with microbes, but it has also become clear that there are limits on the horizon. Some chemical syntheses may be impractical, or even impossible, with a microbe growing in monoculture; however, engineering metabolic processes coordinated between organisms introduces a new set of challenges, such as secretion, diffusion, and regulation of cellular processes between multiple organisms, and maintaining microbial diversity. *Distributed Metabolism* examines these technical research challenges and their potential solutions. One near-term milestone for microbiome engineering is engineering cell transporters that could be used to strategically move intermediate compounds between organisms. Relying exclusively on diffusion across cellular membranes to move compounds is inefficient; therefore, engineering importers and exporters that can facilitate direct metabolite transfer between different species is critical. A long-term milestone is engineering spatially organized microbiomes that contain distinct catalytic environments (e.g., reducing and oxidizing, aerobic and anaerobic), to facilitate complex biosynthetic processes that are challenging even in industrial reactors presently. In addition to considering both synthesis and degradation of compounds using engineered microbiomes, *Distributed Metabolism* also looks at how microbiomes could be designed to share the burden of chemical syntheses, such as engineering one organism to produce reducing equivalents that power reactions in a second organism. Designing processes that use communities of microbes, thus engineering microbiomes, may not only create more efficient processes by introducing different enzyme chemistries, they may also open up entirely new chemical spaces to produce novel materials and compounds (Figure 2).

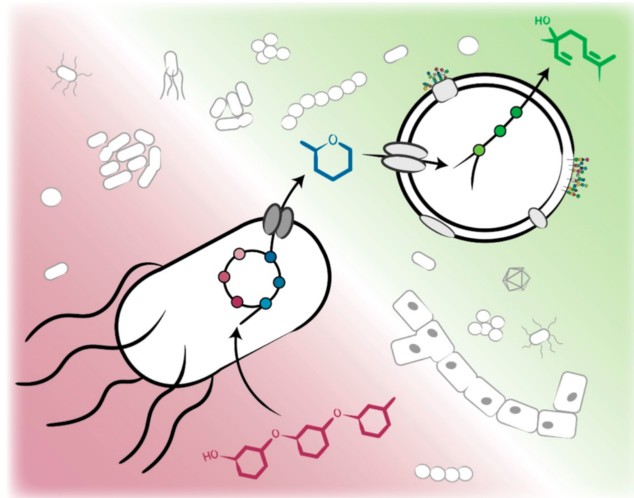

Figure 2. Distributed metabolic processes in an engineered microbiome can facilitate difficult or novel chemical transformations. Production of high-value compounds such as biofuels, solvents, flavorings, and polymers can be facilitated by engineered microbiomes. This community effort toward bioprocessing can lead to more efficient and flexible metabolic processes. In the example illustrated, lignocellulose degradation can be accomplished by one organism within the microbiome, allowing other community members to convert the released sugars into higher-value products, in this case linalool. Further advances will also enable directed metabolic syntheses across disparate environments (e.g., aerobic and anaerobic) that are otherwise impossible using microbial monocultures. Figure reproduced with permission from ref 1. Copyright 2020 Engineering Biology Research Consortium.

Engineering microbiomes will require leveraging expertise across diverse disciplines and creating new tools to culture and characterize microbiomes in the lab and in the field. Fully capturing the dynamics of microbiomes will require large numbers of replicates and many different analytical approaches (i.e., genomics, metabolomics, transcriptomics, proteomics), increasing the cost and complexity of any experiment. A sufficiently powered experiment would then produce data across such wide physical scales, from genomic DNA to the location of cells across meters of space, that novel mathematical and computational methods will be needed to model microbiome composition and function.

Despite these challenges, engineering microbiomes opens up significant opportunities for engineering biology, and for science as a whole. Engineered microbiomes have the potential to revolutionize human and animal health care and wellbeing; ensure, establish, or regulate plant productivity and fitness; redesign and reinvigorate chemical production; transform energy generation; and recalibrate and reclaim the environment through harnessing and engineering the diversity of microbial life. Such innovations must proceed with collaboration among multiple disciplines of science—from ecology to agriculture to medicine to social science—and will require corresponding policy innovations to reduce regulatory uncertainty and promote safety and security of these transformational advancements. *Microbiome Engineering* identifies the pressing challenges in microbiome research and presents a framework for policymakers and funding agencies to drive innovation in microbiome engineering and achieve these cutting-edge capabilities.

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E.D.L. and E.R.A. wrote the manuscript with contributions from the EBRC Microbiomes Roadmapping Working Group. D.C.F. contributed to the manuscript and oversaw its production.

Notes

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