**Transforming medicine with the microbiome**

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Advances in microbiome research are spurring the development of new therapeutics for a variety of diseases, but translational challenges remain.

The study of microorganisms has been revolutionized by complementing the centuries-old art of microbiology with next-generation sequencing of complex bacterial communities (collectively termed “the microbiome”) within and around the eukaryotic host. Microbiome research initially focused on associations between certain microbial compositional features and human medical conditions. The field has quickly evolved, unraveling causative links between distinct microbial consortia, their collective functions, and impacts on host pathophysiology. In addition to the microbiome’s emerging role as an orchestrator of biological processes, it also has plasticity in its composition and function, thereby constituting an attractive target for therapeutic intervention. In this Focus, the first in a special series to celebrate the 10th anniversary of *Science Translational Medicine*, we introduce a paper published in the journal a decade ago and discuss progress in developing translational approaches involving the host-microbiome interface (Fig. 1).

**HOST-MICROBIOME MODULATION BY DIET**

For decades, nutritional research focused on seeking direct links between dietary constituents and human health, aiming to establish universal guidelines to combat disease. However, a large body of research has not resulted in conclusive findings, contributing to various unsubstantiated nutritional trends and unsupported practices. Gut microbiome studies have added an important facet to nutritional research by incorporating the microbiome as a major contributor to host metabolic phenotypes, thus clarifying some of the unresolved questions in the field. In their pioneering work published a decade ago, Turnbaugh et al. (1) showed that host adiposity could be modulated by the gut microbiome’s ability to harvest energy from food; transplantation of microbiome consortia obtained from lean or genetically obese mice into germ-free mice transferred the donor’s phenotype to the recipient animal. In subsequent work published in *Science Translational Medicine* (2), these investigators demonstrated in germ-free mice transplanted with fecal microbiomes from human volunteers that microbiome composition and function could be rapidly and reproducibly altered by diet. These discoveries have led to potential approaches to treat cardiometabolic disease, and attempts have been made to find prebiotic dietary components to shape the microbiome and confer health benefits on the host. An example of such prebiotic intervention was described by Zhao et al. (3); they showed that dietary fiber intake improved glycemic control in patients with type 2 diabetes mellitus to a greater extent than standard care through modulation of the microbiome. With these examples of “one size fits all” nutritional interventions notwithstanding, heterogeneity among individuals in gut microbiome composition and function is increasingly appreciated to hamper universal food-based interventions. Accordingly, Zeedi et al. (4) showed that glycemic responses to food were person specific and dictated by a combination of clinical, laboratory, and microbiome characteristics. Individual postprandial glycemic responses became predictable with a machine-learning algorithm, enabling personalized diets that maintained normoglycemia.

In the next decade, microbiome-based dietary and prebiotic interventions may emerge as essential tools for health care and dietary planning, enabling precision therapies, for example, as a complementary preventive treatment of uncontrolled inflammation in inflammatory bowel disease (IBD). Fecal microbiome profiling could become a component of medical evaluation, leading to tailor-made diets or ad hoc medications. However, conclusive evidence of prebiotic and personalized diets as inducers of sustained metabolic improvements in humans still remains to be determined. Future studies should concentrate on long-term impacts and safety of such therapies and on their potential extension to health conditions beyond obesity and its metabolic complications, such as malnutrition, dietary constituent deficiencies, inflammatory states, and neoplastic diseases.

**HOST-MICROBIOME MODULATION BY PROBIOTICS**

Bacterial supplements, termed probiotics, have been used to promote health for more than a century, yet their efficacy remains inconclusive. Gut microbiome research offers an opportunity to study live microbial interventions in terms of colonization, interactions with the indigenous microbiome, and impact on the host. Recent work (5) suggests that some inconsistencies regarding live microbial effects on the human host might stem from inter-individual differences in probiotic gut colonization patterns and their impact on the indigenous microbiome. As “resistance” and “permissiveness” to probiotic gut mucosal colonization could be predicted by baseline host and microbiome features, an opportunity emerges for context-specific tailoring of distinct probiotic strains to optimize gut colonization and downstream activity.

There are still major obstacles to implementing live microbial therapy in clinical practice. These challenges include the need to develop noninvasive approaches for direct sampling of the gut mucosa and technologies to enable reliable characterization of the microbiome in different regions of the gut. In addition, we need to determine mechanisms of activities of probiotic strains in vivo, thereby enabling the prediction of alterations in the microbiome after treatment. Last, we need to generate high-quality and conclusive clinical data in the form of large multicenter randomized, placebo-controlled trials in different clinical scenarios and human subpopulations.
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pies is to use supplements of bacteria-derived
 HOST-MICROBIOME MODULATION BY FMT
One of the oldest microbiome-based inter-
ventions in humans, which dates back to the
fourth century, is fecal microbiome transplanta-
tion (FMT). In a landmark study, van Nood et al. (9) found that in-
traduodenal infusion of a healthy fecal mi-
metabolites admin-
host microbiomes, and elucidate gut colo-
tering renewed attention because they can target
microbiome (pathobionts) from the ecosys-
with the emergence of antibiotic-resistant bac-

TARGETED ELIMINATION AND GUT BARRIER REGULATION
One unmet need is an intervention that spe-
cifically eliminates harmful members of the
microbiome (pathobionts) from the ecosystem. Although antibiotics are commonly used against pathogens, they are nonspecific, in-
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Fig. 1. Gut microbiome–based therapeutic approaches. Recent research has elucidated gut microbiome interven-
tions for promoting human health and for combating disease. These approaches include microbiome modulation or
direct impact on the host through nutritional intervention, either by prebiotics or by individualized diets (top left). Strategies to affect the gut microbiome or directly impact the host through live bacteria supplementation or exclusion include fecal microbiome transplantation (FMT), treatment with custom-made probiotics, or targeted elimination of bacterial members of the microbiome (top right). The host and potentially its microbiome can also be modulated
by administration, reduction, or activity blocking of bacteria-derived metabolites through treatment with or inhibi-
tion of postbiotics (bottom right) or by manipulation of host gut barrier function (bottom left). Collectively, these
modalities, when used alone or in combinations, will affect the host-microbiome interface.


HOST-MICROBIOME MODULATION BY BACTERIAL METABOLITES
Another strategy for microbiome-based ther-
pies is to use supplements of bacteria-derived metabolites or to block their generation, rather than attempting to enrich or deplete the bacteria that produce them. One example of these so-called "postbiotics" was described by Maslowski et al. (6). They showed that short-
chain fatty acids produced by fermentation of dietary fiber by the gut microbiome or those administered exogenously could attenuate gut inflammation in mouse models of colitis. In animal models of recurrent obesity, diminished flavonoids from an altered microbiome drove exaggerated weight regain after successful dieting (7). Postbiotic replenishment of the depleted metabolites mitigated the accelerated weight regain by affecting adipocyte energy expenditure. Similarly, Koeth et al. (8) revealed that the gut microbiome metab-
olizes l-carnitine, a compound abundant in red meat, into the proatherogenic molecule trimethylamine N-oxide. Follow-up studies have tested inhibitors targeting a gut micro-
bial enzyme in this pathway to combat plate-
let hyperreactivity and to decrease the risk of atherothrombotic events, such as myocardial infarction and stroke. Together, these findings highlight the potential of postbiotic therapy with microbiome-derived molecules in animal models. Additional studies are warranted to shed light on the intended and off-target effects of such compounds and to examine their long-term safety in humans.

HOST-MICROBIOME MODULATION BY FMT
One of the oldest microbiome-based inter-
ventions in humans, which dates back to the
use bacterial recognition sites and phage-associated membrane penetration machinery could serve as a strain-specific pathobiont-targeting modality. Although having great potential, bacteriophage therapy faces major challenges, including an inability to recapitulate in vitro antibacterial action in vivo. This could be attributable to dosing issues, phage mutagenesis, interaction with the microbiome, neutralization by host antibodies, or the emergence of phage-resistant bacterial strains. Combinations of phages targeting distinct receptors on pathobionts of interest may offer a solution to some of these issues.

Another underexplored methodology to regulate host-microbiome interactions and microbial immunomodulatory products lies in direct targeting of the host intestinal barrier. Emerging regulators of gut barrier function include biophysical factors such as osmotic pressure, microbiome-generated molecules, and host-related modulators. Comprehensive understanding of the repertoire and mechanisms of these barrier-modulating factors is an exciting avenue of future research.

CHALLENGES AND PROSPECTS

The last decade has witnessed a remarkable leap in microbiome research. In its infancy, such research focused on important but inherently limited descriptive studies, offering a detailed characterization of microbiome alterations during health and disease and in response to distinct dietary regimens. These studies are now being followed by more mechanistic approaches to establish causal links between microbiome assemblages and various phenotypes. A new and exciting aspect of microbiome research focuses on personalization of interventions, as well as harnessing the inherent individualized variability in microbiomes and other physiological features to explain and even predict human health and disease states.

In addition to the specific challenges presented so far, there are some general limitations to be considered when attempting to draw clinical conclusions from gut microbiome research. Conceptual pitfalls include distinguishing between associative and causative relationships, which should be validated by appropriate experimentation. This could be accomplished by ablation of the disease phenotype after antibiotic treatment or by mimicking the phenotype with the administration of a postbiotic compound. The ideal validation would reproduce the phenotype by transplan-

REFERENCES AND NOTES


Acknowledgments: We thank the members of the Eilnai laboratory for helpful discussions. E.E. is a paid consultant at DayTwo and BiomX.

10.1126/scitranslmed.aaw1815

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Sci Transl Med 11, eaaw1815.
DOI: 10.1126/scitranslmed.aaw1815

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