Engineering xxx (xxxx) xxx

Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

Editorial

# Editorial for the Special Issue on the Development of Gut-Microbiome-Targeted Foods and Drugs

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Research on the gut microbiome, which first began to take shape with the advent of culture-independent, high-throughput sequencing, has now evolved into a highly active frontier in the life sciences. It is widely recognized that the gut microbiome is shaped by both host genetics and various environmental factors—including diet and lifestyle—and is closely associated with human physiology and a broad spectrum of diseases. Notably, environmental and lifestyle exposures appear to account for considerably more of the interindividual variation in gut microbiome composition than host genetics, which is precisely what makes the microbiome an attractive modifiable target. These advances have stimulated growing interest in translating gut microbiome research into the development of gut-microbiome-targeted foods and drugs to improve human health. However, such efforts remain challenging because of the complexity of microbiota–host interactions, substantial interindividual variability, and the disconnect between association studies, mechanistic understanding, and clinical efficacy. Against this background, this Special Issue brings together nine contributions that explore fundamental mechanisms, dietary modulation, microbiome heterogeneity, probiotic–drug interactions, and translational opportunities in the development of gut-microbiome-targeted foods and drugs.

A prerequisite for gut-microbiome-targeted interventions is a mechanistic understanding of how the microbiota influences host physiological and metabolic functions. M. Zhang et al. provide an integrated perspective on microbiota–host crosstalk mediated by microbial metabolites, structural components, and extracellular vesicles. Rather than acting independently, these pathways form interconnected regulatory networks that influence metabolism, immune homeostasis, and neuroendocrine function. The authors further emphasize that these effects are strongly dependent on interindividual genetic and immune variability and pronounced spatiotemporal heterogeneity along the intestinal tract. Building on this mechanistic perspective, Attema and Kuipers focus on bile acids, which are key metabolites extensively modified by the gut microbiota and central mediators of the gut–liver axis. The authors argue that microbiota-driven remodeling of the bile acid pool, as well as the signaling through nuclear and membrane receptors that follows from it, links intestinal ecology to systemic physiology, and that targeting this axis may offer opportunities to promote healthy aging and extend healthspan. Complementing these studies, Kuzub et al. extend the traditionally bacteria-centered view of the gut microbiome by reviewing the infant gut virome. They summarize its rapid and highly individualized development during early life, its associations with immune function and disease outcomes, and the major methodological and bioinformatic challenges that remain in gut virome research. Their review makes clear that a complete account of microbiome–host interactions, along with any intervention designed to reshape them, will eventually have to accommodate the viral fraction of the ecosystem.

Another key focus of this Special Issue is dietary modulation: Despite being one of the most practical approaches to shape the gut microbial ecosystem, its effects cannot be fully understood by examining individual nutrients or foods in isolation. Deng et al. introduce the concept of long-term food pairing patterns and, using two large population-based cohorts, show that the balance between foods provides information beyond conventional dietary indices and individual food intake in relation to cardiometabolic health. They further report that close to three quarters of the associations between long-term food pairing patterns and cardiometabolic traits were statistically mediated by gut microorganisms and their metabolic pathways, supporting gut-

https://doi.org/10.1016/j.eng.2026.10.003
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Please cite this article as: Q. Zhai, H. Wu, S. Huang et al., Editorial for the Special Issue on the Development of Gut-Microbiome-Targeted Foods and Drugs, Engineering, https://doi.org/10.1016/j.eng.2026.10.003

microbiome-targeted dietary design that considers food combinations and dietary balance.

Food additives are an additional, far less well-characterized determinant of gut microbial ecology, and they are harder to study because exposure is chronic, low-dose, and rarely isolated from the food matrix. Two contributions to this issue take up that problem. Lin et al. review the effects of natural and artificial food colorants through both microbiota-dependent and microbiota-independent pathways. Several natural colorants may exert beneficial effects through modulation of the gut microbiota and the generation of bioactive metabolites, whereas certain artificial colorants may disrupt microbial homeostasis and contribute to inflammatory or metabolic abnormalities. Cai et al. examine the health effects of artificial sweeteners from the perspective of host response variability and gut microbiota. Their review identifies four potential microbiota-mediated mechanisms: disruption of bile acid homeostasis, modulation of tryptophan metabolism, alteration of short-chain fatty acid levels, and regulation of lipopolysaccharide leakage. They further emphasize that the effects of artificial sweeteners may vary substantially across physiological states and susceptible populations. Together, these studies support a shift in gut-microbiome-targeted food and drug development from one-size-fits-all evaluation toward context- and population-specific recommendations.

Beyond elucidating how diet and food additives shape the gut microbiome, a key translational objective is to improve health through targeted modulation of gut microbial communities or their functions. Z. Zhang et al. show that the efficacy of probiotic treatment for inflammatory bowel disease (IBD) depends strongly on the baseline state of the gut microbiome. Using genetically identical mice with distinct microbial communities, they demonstrate that the distribution of health- and disease-associated microbial guilds influences ecological network stability, probiotic receptivity, the production of indole metabolites, host inflammatory responses, and ultimately treatment efficacy. This study highlights the need for microbiome-informed food and drug interventions tailored to individual microbial profiles and for stratifying participants by baseline microbiome state at the design stage of intervention trials rather than only in *post hoc* analysis. Tian et al. further demonstrate how gut-microbiome-targeted interventions can be developed from a single, well-defined microbial metabolic function. After identifying reduced circulating S-adenosylmethionine (SAM) in patients with insomnia, they screened 60 gut bacterial strains and identified the high-SAM-producing *Lactobacillus helveticus* CCFM1320, which improved sleep-related phenotypes in mice by enhancing melatonin synthesis and circadian signaling. A subsequent 4-week placebo-controlled trial further demonstrated improved sleep quality in patients with insomnia. This study illustrates a translational pathway from biomarker identification and functional strain screening to mechanistic validation and human intervention. Li et al. further extend this translational agenda to probiotic–drug co-administration. Using *Lacticaseibacillus paracasei* Zhang (LCZ) and lovastatin, they first show in vitro that LCZ can convert lovastatin into its active hydroxy acid. In hyperlipidemic golden hamsters, however, the improved anti-hyperlipidemic efficacy of low-dose lovastatin plus LCZ is primarily explained by LCZ-induced changes in the gut metabolite environment that enhance lovastatin solubility and absorption, rather than by direct intestinal conversion; increased absorption is accompanied by upregulation of hepatic bile acid metabolism and drug-transformation genes. Importantly, the interaction is dose-dependent, with medium- and high-dose lovastatin plus LCZ increasing systemic exposure and toxicity. This study adds a safety and dose-awareness dimension to probiotic–drug co-treatment and supports strain-resolved, individualized strategies for microbiome-targeted food–drug development.

Collectively, the articles presented in this Special Issue reflect an important transition in microbiome research, from describing microbial community composition to understanding microbial functions and ecological interactions, and ultimately to the rational design of microbiome-targeted foods and drugs. At the same time, they highlight several challenges that must be addressed before microbiome-based interventions can be widely implemented: Baseline microbiome heterogeneity should be incorporated into efficacy evaluation; microbial metabolites and interspecies interactions require deeper mechanistic resolution; taxonomic resolution below the species level and absolute rather than relative quantification are needed before host effects can be attributed to specific organisms; viruses and other non-bacterial components of the microbiome warrant greater attention; and findings from experimental models need rigorous validation in humans and in independent cohorts that differ in ancestry, diet, and geography. Advances in multi-omics, high-resolution population studies, synthetic microbial communities, synthetic biology, and artificial intelligence will increasingly enable causal hypotheses to be generated and tested at scale and individual responses to be predicted, thereby advancing precision nutrition and precision medicine.

We sincerely thank all authors for their contributions to this Special Issue. We also acknowledge the reviewers and the editorial team for their rigorous and efficient work. We hope that the findings and perspectives presented in this collection will stimulate further interdisciplinary research and accelerate the translation of gut microbiome research into effective foods, drugs, and strategies for promoting human health.