Microbiome-Based Therapeutics: Emerging Trends in Health Biotechnology

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ABSTRACT

Recent technological advancements have allowed for a thorough examination of the human microbiome, leading to the discovery of certain microbial patterns that are linked to health and disease. This validates the essential function of bacteria in preserving homeostasis and the overall health condition of the host. In this review, we thoroughly analyze the present state of microbiome-based medicines, including established and developing techniques. We explore the mechanisms of action of these therapies, their applications, and the associated problems. In addition, we outline the challenges faced by the scientific community in the advancement of microbiome therapeutics. Investigations into the human gut microbiome have expanded our knowledge of how microorganisms establish, develop, and become imbalanced in different states of health. Microbiome therapies include manipulating the gut microbiome by using various treatments, such as adding, removing, or modifying the bacteria. This may be done using natural or modified microorganisms, antibiotics, bacteriophages, and bacteriocins. This strategy has the potential to surpass the restrictions of traditional treatments by offering individualized, coordinated, dependable, and enduring therapy. Although promising, microbiome therapies are still in the early stages of development and face many technical and administrative challenges. These challenges include optimizing microbial therapies for specific body parts, identifying appropriate biosensors, establishing the resilience of engineered synthetic gene circuits, and addressing biosafety concerns.

Keywords: Microbiome therapy, Gut microbiome, Fecal microbiota transplantation (FMT), Phage therapy

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Introduction

In recent decades, researchers have uncovered several connections between microbiota and the health of the host. The human microbiome encompasses all the bacteria and derived metabolites present within and on the human body.[1] The microbiota residing in the gut, oral cavity, nasal cavity, skin, and vagina maintain a delicate equilibrium that facilitates digestion, nutrient acquisition, and protection against pathogens, thereby, contributing to the homeostasis of the host.[2] The microbiome is not merely a passive observer; it actively influences multiple processes within the host body, including circadian rhythm, nutritional responses, metabolism, and immunity.[3] The microbiome significantly impacts the programming and development of key components of the host's innate and adaptive immune systems.[4,5]

The relationship between therapeutics and microbiota is bidirectional, with each influencing the other. A recent pharmacological study found that approximately 25% of over 1,000 non-antibiotic drugs tested exhibited antibacterial properties when evaluated against 40 types of human gut flora.[6] Another study revealed that out of 271 drugs tested on 76 human gut bacterial species, 176 significantly inhibited bacterial growth by more than 20%.[7] Additionally, research employing high-throughput genomic analysis and mass spectrometry has identified causal links between microbiota and variations in microbiomes, which contribute to individual differences in drug metabolism.[4,8] These findings have profound implications for the identification and understanding of the non-target effects of a broad range of medications.

Microbiome therapy offers several advantages over conventional therapeutics. Microbes are indigenous inhabitants of the human body, and their therapeutic potential can be harnessed with minimal adverse side effects. Recent research demonstrates that *Christensenella* spp. can reduce symptoms of depression and anxiety. Additionally, *Akkermansiamuciniphila* has been shown to alleviate metabolic diseases and enhance the efficacy of metformin in cancer treatment. This microbe also protects against atherosclerosis by reducing intestinal permeability and inhibiting inflammation.[8,9] *Lactobacillus johnsonii* offers protective effects against cancer, while *Bifidobacterium longum* mitigates the severity of Crohn's disease and restores the integrity of the mucus layer compromised by a high-fat diet.[3] *Oxalobacter formigenes* maintains the balance of oxalic acid, thus preventing the formation of kidney stones, and *Bacteroides* species confer protection against obesity.[10,11]

Numerous studies have established the crucial role of the microbiome in both health and disease. Microbiome-based therapies can be broadly categorized into three paradigms: 1) additive, 2) subtractive, and 3) modulatory therapies.[12] Additive therapy involves the enhancement of host microbiota through the introduction of specific strains of microorganisms, which may be natural or genetically modified, while subtractive therapy entails the targeted removal of pathogenic microorganisms from the microbiome to treat a disease. Modulatory therapy, on the other hand, involves the use of non-living substances, such as prebiotics, to alter or regulate the composition or behavior of the host microbiome. Probiotics and prebiotics represent the earliest forms of microbiome therapy and have been extensively studied.[13,14]

Microbial diversity varies across different body sites, and the complexity and function of bacterial communities are influenced by factors such as health status, genetics, diet, and hygiene practices.[5]

The environmental and biological characteristics of each body habitat significantly influence the microbial richness and genetic diversity of the associated microbiomes.[15] Although yeast and viruses are integral components of the human microbiome, most research has focused predominantly on host-associated bacteria. Microbial dysbiosis is associated with various human health conditions, including obesity, inflammatory bowel diseases (IBDs), autoimmune disorders (e.g., rheumatoid arthritis), and mental health issues such as stress and Alzheimer's disease. Dysbiosis of the gut, oral, or skin microbiomes is also linked to conditions like periodontal disease, acne, and eczema.[16,17] In this review, we explore the most recent developments in microbiome-based medicines, different types, and the processes through which these medicines operate.

Microbiome-Based Therapeutics: Categories and Mechanisms

Probiotics

According to the Food and Agriculture Organization/World Health Organization (FAO/WHO), probiotics are "live microorganisms that, when used in adequate amounts, provide health benefits to the host." Probiotics are components of foods like milk and curd and have been used throughout history. These fermented foods contain a mix of bacterial strains like bifidobacteria, lactobacilli, and other lactic acid-producing bacteria that provide beneficial effects when used under certain specific circumstances.[18] This fact led to the development of modern probiotics involving the administration of controlled doses of live, purified bacteria.[4] Genetic and molecular studies have shown that the beneficial effects of probiotics on the host are conferred by four basic mechanisms (Figure 1): 1) by producing antimicrobial substances, 2) competing with pathogens for nutrients and for adhesion to the epithelium, 3) immunomodulation of the host, and 4) prevention of bacterial toxin production.[19,20]

Probiotics have been used to treat several ailments in humans, including IBD, diarrhea, Crohn's disease, ulcerative colitis, and cancer. Besides this, several studies demonstrate the positive impact of using probiotics in the treatment of diseases like lactose intolerance,[4] and in the prevention of colorectal cancer and peptic ulcers.[21] Although probiotic bacterial strains are effective in the treatment of several diseases, their use can be harmful if administered after antibiotic treatment.[22] The progression of the disease, microbiome composition before treatment, and timing of the treatment administration are some of the causative factors of non-responsiveness to the probiotic treatment.[23]

Prebiotics

Prebiotics are substances that are preferentially used by the microbiome, are easily administered, and provide health benefits to the host by supporting beneficial bacteria. Their beneficial effects are highly dependent on their physiological properties. They are classified based on their properties as: 1) not digested, 2) not absorbed in the small intestine, 3) well fermented by intestinal bacteria, 4) poorly fermented by intestinal bacteria, and 5) poorly fermented by the bacteria of the oral cavity.[19,22]

Prebiotics are naturally found in small amounts in various food items and can be obtained in a variety of natural or artificial forms, such as dietary fibers, resistant starches, pyrodextrins, lactulose, inulin, and oligosaccharides.[24] Fructo-oligosaccharides (FOS) and galacto-oligosaccharides are the most studied prebiotics. They are known to exert their beneficial effect by increasing the Bifidobacteria within the gut. Both are routinely administered through infant formula to newborns.[10]

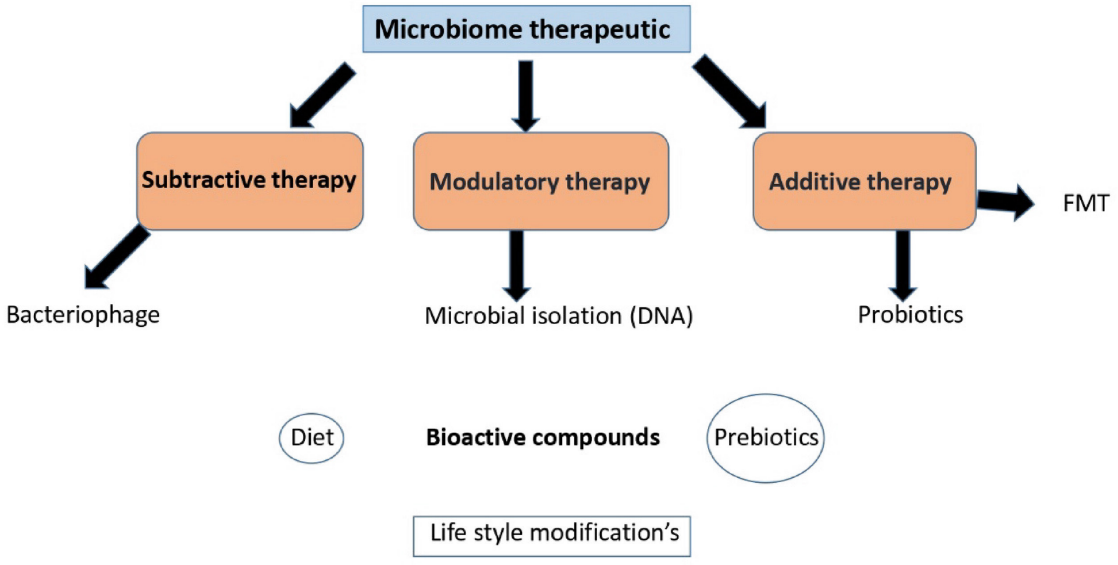

Fig 1 | Overview of the different types of microbiome-based therapeutics

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The gut microbial ecology is influenced by the "substratum cross-feeding effect" mechanism, in which by-products obtained by the breakdown of prebiotic fibers are used by other beneficial bacteria. The butyrogenic impact, in which the acids produced during the fermentation of prebiotics alter the environment, is a prime illustration of the cross-feeding phenomenon. Prebiotics also help in reducing blood low-density lipoprotein, maintenance of intestinal pH, immunological modulation, and increased calcium absorbency.[19]

Prebiotics can alter the makeup of the gut microbiota. For example, in patients with IBD, prebiotics can improve the composition of the gut microbiota and reduce gastrointestinal tract inflammation. Moreover, prebiotics are helpful against pathogenic microorganisms, such as *Salmonella enteritidis* and *Escherichia coli*, and in cancer treatment.[25,26] However, it should be kept in mind that even small doses of prebiotics can sometimes cause side effects either due to the production of gasses by rapid prebiotic fermentation or by prebiotic-induced osmotic changes in the gastrointestinal tract.[27] Further, if the patient is colonized with bacteria that can metabolize the treatment, it could lead to non-responsiveness to the probiotic treatment.[28] The augmentation of the prebiotics to feed the current microbiota population along with the therapies that provide the beneficial bacteria directly could cumulatively help to improve the patient's outcome.

Synbiotics

Synbiotics are defined as probiotics combined with certain prebiotics to give a synergistic mixture that provides beneficial effects to the host by improving the survival and colonization of gut microbiota.[29] There are two main sub-groups of synbiotics: 1) synergistic synbiotics and 2) complementary synbiotics. In synergistic synbiotics, prebiotics provide nutrients to the probiotic, while in complementary synbiotics, prebiotics support the growth and survival of microbiota.[30] Studies have shown the efficacy of synbiotics in the treatment of various illnesses, including the use of *Bacillus coagulans* and FOS in Inflammatory Bowel Syndrome (IBS); a combination of *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* strains, and FOS in non-alcoholic fatty liver disease, and using *B ifidobacterium lactis* B94 in diarrhea.[31] Similarly, several meta-analysis studies on adults have supported the positive effects of synbiotics on constipation, on lowering of blood glucose levels, and on the risk of developing postoperative sepsis.[31,32]

Fecal Microbiota Transplantation (FMT)

FMT is the procedure to administer a solution of fecal matter from a healthy donor into the intestine of a recipient to change the recipient's microbial composition and provide health benefits to the recipient (Figure 2).[33] This process involves the selection of appropriate donors that do not have any family history of autoimmune, malignant, or metabolic diseases and any potential pathogens. The solution of the donor's feces is prepared in water or normal saline, filtered, and administered through colonoscopy, nasogastric tube, nasojejunal tube, or esophagogastroduodenoscopy.[34] FMT has traditionally been used in ancient China and Indigenous Australian culture for healing purposes. Nevertheless, its potential as a modern treatment has only been acknowledged over the last two to three decades.[35]

FMT is safe and effective in treating patients with *Clostridium difficile* infection (CDI) in more than 70 clinical studies, with reported success rates ranging from 85% to 95%. FMT is thought to increase the diversity and abundance of bacteria in the gastrointestinal system through *C. difficile* and avert reinfection.[36]

A study conducted by Philips et al.[37] has shown that patients with severe alcohol-associated hepatitis due to long-term, high-dose alcohol consumption may potentially derive the largest degree of benefit from this novel FMT therapy. He conducted one of the first pilot trials comparing the effects of FMT on eight male patients with severe alcohol-associated hepatitis to a group of 18 controls with the same condition who received standard-of-care treatment over 7 days.[37] The FMT arm showed a substantial improvement in liver disease severity indices and survival rates compared to the conventional treatment arm. These findings indicate that FMT enhances longevity beyond the benefits provided by existing treatments and might serve as a cost-effective means of facilitating liver transplantation. Another research has shown that the FMT may have the ability to decrease alcohol demand and intake, as well as prevent long-term hospitalizations associated with alcohol use disorders.[38]

In this unblinded, randomized controlled crossover study, the typical therapy group had a 50% recurrence rate, while the FMT arm showed no recurrence. FMT therapy demonstrated not only long-term safety and efficacy, with effects maintained for 1 year, but also resulted in an increased variety of microorganisms in the engrafted feces and the number of helpful bacteria Lactobacillaceae and Bifidobacteriaceae.[38] Further, FMT is a successful treatment method for antibiotic-induced dysbiosis in *C. difficile* infections. It has exhibited high efficacy in treating patients with recurrent *C. difficile* infections.[39] Many clinical studies are being conducted to assess FMT potentials to reduce or eliminate antibiotic-resistant bacteria in the digestive system.[40] Alcoholic hepatitis and cirrhosis are both associated with a shortage of mucosa-associated invariant T lymphocytes. The recovery of these T-cells was found in patients after FMT. [41]

Researchers are now studying the potential application of FMT therapy in immunological-related disorders because of the microbiome's substantial impact on the immune system. These disorders include acute graft-versus-host disease (GVHD), Type I diabetes, and multiple sclerosis. The outcomes of these investigations have shown variability; overall, they have shown promise, especially in the management of GVHD.[42] A recent study indicated that gut microbiota plays a crucial role in metabolizing foreign medicines and regulating immune responses, which has significant implications for cancer therapy. For example, FMT can

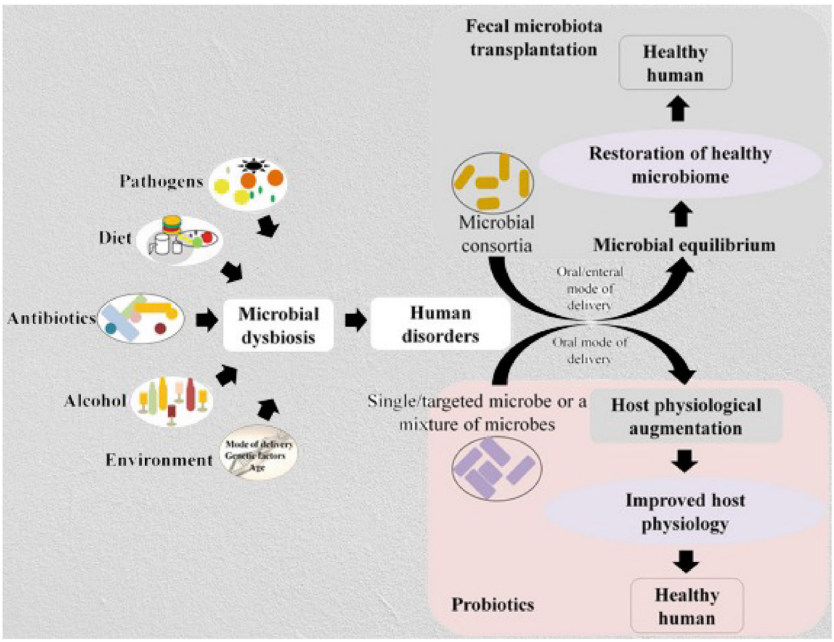

Fig 2 | Distinction between the activities of FMT and probiotics in the treatment of human illnesses

enhance the efficacy of immunotherapy and alleviate the adverse effects of chemotherapy. These results indicate that microbiome-based treatments have the potential to become the primary method to tailor anticancer medicines in the future.[5]

Phage Therapies

The global decline in the efficacy of antibiotics has fostered interest in looking for other alternative strategies for prophylaxis and control of infectious diseases. Recently, technological advancements, like next-generation sequencing and electron microscopy, have sparked a revival in phage therapy research. Phage therapy is the use of bacteriolytic phages to treat bacterial infections.[43] The use of bacteriophages as solitary therapeutic agents dates back more than 100 years.[44] As an alternative treatment, phage therapy is being supported due to several advantages phages have over antibiotics, including self-amplification, biofilm degradation, host-specificity, and low toxicity to humans.[45] This therapy could not only be administered as a sole alternative to antibiotics but also as a combination with them.[46] A recent study demonstrated synergistic potential and a reduced acquisition of resistance in bacteria.[47]

In a clinical trial, phage cocktails specifically prepared against difficult-to-treat *E. coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* infections, as well as multidrug-resistant bacterial diseases such as methicillin-resistant *S. aureus* or *Acinetobacter baumannii*, have shown promise. It has been demonstrated that active phages contribute to positive outcomes of therapy by colonizing the host following FMT.[48] Another study suggested that the effectiveness of the sterile filtrate of FMT in patients with CDI may be partially due to phages.[49] Host specificity of the phage offers an opportunity to specifically reduce the population of infection-causing pathogen bacteria, preserving beneficial microbiota. Therefore, the composition and role of indigenous microbiota must be taken into consideration while planning phage therapy.[47]

Engineered Microbiomes and Synthetic Biology

Microbiome engineering has entered a new era with the advent of synthetic biology, as it enables the construction of tailor-made microbial strains with important therapeutic applications. Whole-genome editing with CRISPR-Cas9 is being extensively used to genetically engineer microbial genomes, thereby improving or obtaining various bacterial characteristics that can be used to treat diseases.[50] Genetically engineered bacterial strains are used to produce the cytokine interleukin-22, which plays a key role in maintaining gut barrier integrity and helps to control immune responses. The administration of this engineered bacterial strain to models of IBD not only resulted in a reduction in gut inflammation but also a considerable improvement in mucosal lining. These results suggest that it could serve as a therapy for Crohn's and other conditions such as ulcerative colitis.[51]

Microbiome-Derived Metabolites

The gut microbiota produces a wide variety of compounds that are used both by the host as well as by other microorganisms. These interactions between the organisms, termed host–microbe and microbial community interactions, are important to shaping the host microbial symbiosis and the establishment of stable microbiota communities to promote host health.[7,11] Microbiome mimetics are interventions that replicate the interactions between the microbiome and host, leading to beneficial therapeutic outcomes. These include traditional therapies, bacteria-derived products, small molecules, or host-derived products.[52] The majority of the health benefits conferred by the administration of probiotics and prebiotics are due to the production of components like functional proteins, microbial fractions, secreted polysaccharides, cell lysates, teichoic acid, and pili-type structures,[23,53] which gave rise to the concept of "postbiotics," the newest member of the "biotics" family. Other studies used the terms "paraprobiotics," "non-viable microbial cells," and "fermented infant formulas" (FIFs) for postbiotics. Postbiotics are fermentation compounds that can be used in combination with nutritional components to provide health benefits.[54] The two most common classes of postbiotics are para-probiotics, which are non-viable components of bacteria (bacterial proteins and polysaccharides), and FIFs, which are purified products produced after the infant formula is fermented by lactic acid-producing or other bacteria.[55] Postbiotics are based on proteins, lipids, carbohydrates, metabolites, vitamins, organic acids, cell wall components, and other molecules secreted during fermentation. Hence, their composition could vary by methods used for food processing such as heat,

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Table 1 | Examples of Postbiotics

Microbial-Metabolite Pathways	Bacterial Transformation	Examples of Clinical and Translational Investigations in Liver Disease
Bile acids	Deconjugation: bile salt hydrolases. Secondary bile acid formation: 7-alpha dihydroxylation.	Notable alterations with the course of alcohol-associated liver disease and after alcohol use is stopped. Effects resulting from the use of Farnesoid X Receptor (FXR) modulators, Fecal Microbiota Transplant (FMT), or rifaximin.
Choline compounds Trimethylamine N-oxide (TMAO)	Multiple taxa break it down to trimethylamine (TMA), which is further oxidized to TMAO in the liver.	Linked to metabolic syndrome. Pre-transplant, there is a decrease, but after a liver transplant, there is a recovery.
Short-chain fatty acids	Dietary fiber and intestinal mucus fermentation.	Differential effects on obesity and responsiveness to high-fat diet fluctuate in response to lactulose intake. Repaired/improved after Fecal Microbiota Transplant (FMT).

pressure, sonication, and irradiation, and it can affect the efficacy of postbiotics (Table 1).[56]

Short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate produced by bacterial fermentation are the most commonly used postbiotics. It has been found that SCFAs have beneficial effects on the mucosal immune system and are also found to be efficient in delaying the onset of type 1 diabetes mellitus in mice.[55,57] Future microbiome therapies may include the augmentation of dietary intervention to provide beneficial effects through microbiota that will help to bring closer the concept of personalized treatment by integrating the knowledge from food and microbiology.

Scientific Challenges to the Adoption of Microbiome-Based Therapeutics

Consistency and Stability of Microbial Products

Despite their immense potential, microbiome-based therapies face several significant challenges to widespread adoption (Figure 3). The primary concern with the broader application of microbiome-based therapeutics is the incomplete understanding of their mode of action. Although we have studied the human microbiome, the interactions between microbial communities and the host are still in their early stages. Therefore, it is difficult to predict how altering the microbiome may affect the host's health and physiology.[58] Additionally, understanding the delicate interactions between microbiome and host immune responses requires more research.[5] Furthermore, small variations in the manufacturing processes of the same microbe-based medicine can result in inconsistent products and in turn different outcomes. On the other hand, maintaining the function of live microorganisms in different environments, from storage to the human gut, can be a very difficult task. Therefore, to keep microbial products viable and effective over time, we need to develop robust preservation and delivery methods.[59]

Biosafety Concerns

Biosafety is a prerequisite for using live or genetically modified microorganisms because introducing live microbes into the human body poses a risk of non-target effects. These non-target effects include, but are not limited to, horizontal gene transfer between therapeutic microbes and native microbiota. Such an event can lead to the development of antibiotic resistance and

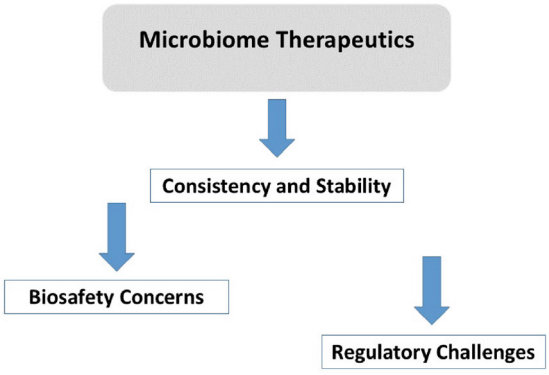

Fig 3 | Challenges associated with the adoption of microbiome therapeutics

many other harmful traits in the native microbiota.[60] Additionally, there is always potential for engineered microorganisms to evolve within the host environment. Therefore, there is a need to devise strict containment strategies to ensure that these organisms do not spread beyond specified limits. Hence, careful implementation of biosafety protocols is critical for the safe commercialization of microbiome therapies.

Regulatory Challenges

Finally, the regulatory landscape for microbiome-based therapeutics is still evolving. Traditional regulatory frameworks, developed for small-molecule drugs and biologics, are not ideal for this class of therapeutics.[28] The U.S. Food and Drug Administration and European Medicines Agency are issuing guidance for these therapies. However, gaps remain in the acceptable definition of quality standards, manufacturing consistency, and post-market monitoring. Regulatory agencies should also devise protocols for evaluating the long-term safety and efficacy of microbiome therapies. Considering their potential to interact unpredictably with the host's native microbial communities, they can cause unintended, non-target effects in the host as well as wider society.

Conclusion

Microbiome-based therapeutics include prebiotics, probiotics, live microorganisms, microbiome mimetics, and others. All of them have their unique composition and

mode of action in the host body. Using modern techniques such as bioinformatics, genetic engineering, metagenomics, and metabolomics can give a whole new direction to this therapy. We can experience oral, FMT, and site-specific microbiome medicines. In the near future, there is a huge potential for person- and disease-specific, genetically modified microbiome therapeutics. This can revolutionize the treatment methods and the overall health management. The main obstacles currently encountered include identifying clinical conditions that may be effectively treated with microbiome-based medications and developing suitable approaches to discover, improve, and evaluate potential therapeutics. Although targeted therapeutics, such as modified bacteria, postbiotics, and phages, have been tested in several preclinical settings, their full effectiveness and safety remain to be evaluated. Most current studies focus on short-term outcomes; there are limited clinical data on the safety and effectiveness of long-term use of microbiome-based therapies. We are of the view that there is a need for post-market surveillance and long-term risk assessment of these therapies. Without these data, regulatory approval and patient confidence in microbiome-based therapies will remain limited. More randomized controlled trials on larger cohorts are needed to build a durable foundation for the wider adoption of microbiome therapeutics.

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