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# Harnessing the microbiota for therapeutic purposes

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## Funding information

TL is funded as postdoctoral fellow by the German Research Foundation (DFG, 420943353).

The myriads of microorganisms colonizing the human host (microbiome) affect virtually every aspect of its physiology in health and disease. The past decade witnessed unprecedented advances in microbiome research. The field rapidly transitioned from descriptive studies to deep mechanistic insights into host-microbiome interactions. This offers the opportunity for microbiome-targeted therapeutic manipulation. Currently, several strategies of microbiome-targeted interventions are intensively explored. Best evidence from human randomized clinical trials is available for fecal microbiota transplantation (FMT). However, patient eligibility as well as long-term efficacy and safety are not sufficiently defined. Therefore, there is currently no officially approved indication for FMT. Probiotics (live microorganisms) have long been discussed as a means to aid human health but have yielded varying results. Emerging techniques utilizing microbiota-targeted diets, small microbial molecules, recombinant bacteriophages, and precise control of strain abundance recently yielded promising results but require further investigation. The rapid technological progress of “omics” tools spurs advances in personalized medicine. Understanding and integration of interindividual microbiome variability holds potential to promote personalized preventive and therapeutic approaches. Emerging evidence points towards the microbiome as an important player having an impact on transplantation outcomes. Microbiome-targeted interventions have potential to aid against the many challenges faced by transplant recipients.

## KEYWORDS

animal models, bioengineering, clinical research/practice, genomics, immune regulation, immunobiology, immunosuppression/immune modulation, infection and infectious agents, infectious disease, translational research/science

## 1 | INTRODUCTION

The introduction of molecular-phylogenetic techniques to study microbial ecosystems in addition to traditional cultivation-based methods has revealed an enormous microbial diversity in the biosphere.

**Abbreviations:** ALS, amyotrophic lateral sclerosis; APC, antigen-presenting cell; CD, Crohn's disease; CDI, clostridioides difficile infection; EcN, *Escherichia coli* Nissle 1917; FDA, Food and Drug Administration; FMT, fecal microbiota transplantation; GPCRs, G-protein-coupled receptors; IBD, inflammatory bowel disease; RCT, randomized clinical trial; SCD, specific carbohydrate diet; SCFA, short-chain fatty acids; UC, ulcerative colitis; VMT, vaginal microbiota transplantation.

Humans have coevolved with complex microbial communities colonizing the metazoan host, collectively termed “microbiota” or “microbiome.” The microbiota's collective genome (“metagenome”) is now recognized as a key regulator of the host's physiology in health and disease, modulating complex biological systems such as immunity and metabolism.<sup>1</sup> Humans are virtually identical in their genetic makeup, yet the relatively small interindividual genomic differences give rise to important phenotypic differences. In contrast, the interindividual diversity of the metagenome is considerably larger with only a third of its genes found in the majority of healthy subjects.<sup>2</sup> Moreover,

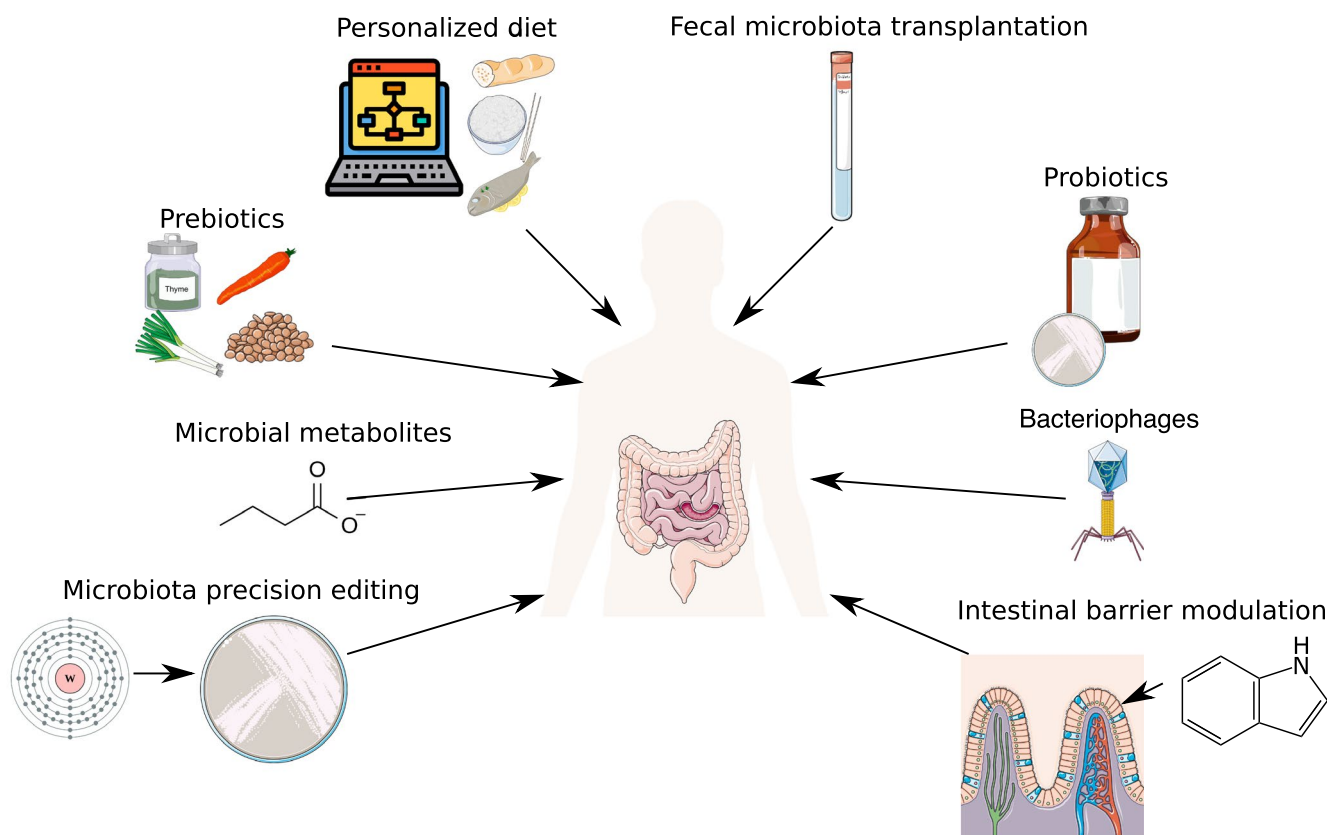
although the individual human genome remains largely stable, the taxonomic composition and metabolic functions of the microbiome can be modulated by external factors, most notably diet.<sup>3</sup> Numerous studies documented microbial alterations of the intestine and other organ surfaces in a growing number of diseases.<sup>4</sup> The microbiome's variability and plasticity make it a promising research target to understand the pathogenesis and identify therapeutic targets for many human diseases. During the past decade, the field of microbiome research has rapidly evolved, transitioning from largely associative analyses to detailed reductionist mechanistic studies deciphering the causal links between the microbiome and the host's biological processes.<sup>4</sup>

In this review, we summarize recent progress in translating microbiome research into therapeutic interventions with emphasis on immunity and inflammation (Figure 1). Given the large number of potentially relevant preclinical studies, the present article focuses on selected literature directed toward clinical applications and related basic research. At the end, we suggest how manipulating the microbiome may advance transplantation medicine.

## 2 | DIET

Diet strongly affects human health, partly by modulating the gut microbiota. Diet has a long-term deep impact on the gut microbiota structure and drives convergence in gut microbiota functions across mammalian phylogeny and between humans.<sup>5</sup> A switch between an animal-based and plant-based diet rapidly and reproducibly induces changes in the gut microbiome composition.<sup>3</sup> Noncaloric artificial sweeteners, which have no primary nutritional value to the host, may drive glucose intolerance through induction of compositional and functional alterations of the gut microbiome.<sup>6</sup> The relationship between diet and the microbiota is mutualistic; in this way the gut microbiome determines the host's individual glycemic responses to diet.<sup>7</sup>

Many effects of diet on host biology are mediated via food-derived microbial metabolites.<sup>8</sup> These metabolites may confer health benefits through regulation of local and systemic immunity. Fiber-derived fermentation products, including the short-chain fatty acids (SCFA) butyrate, acetate, and propionate, exert a wide array



**FIGURE 1** Microbiota-targeted therapeutic approaches. Recent advances in microbiome research forged new paths for microbiome-targeted interventions aiming at promoting human health. The approaches include modulation of gut-microbiome composition by dietary interventions. These can consist in personalized nutrition tailored after computational analysis of a sufficient array of the individual's data, including gut microbiome parameters. Another dietary approach is consumption of prebiotics, dietary compounds aiming at specifically fostering microbes with presumed beneficial properties. Fecal microbiota transplantation aims at treating diseases via replacement of an entire perturbed microbiota by a presumably balanced, healthy microbiota. Probiotics are live microorganisms that are intended to confer a health benefit to the host. The supplementation of particular metabolites, such as butyrate, produced by beneficial microorganisms circumvents the challenges associated with engrafting live microorganisms. Engineered bacteriophages are a promising means for targeted depletion of foreign pathogens or commensal microbiota members considered harmful. Emerging approaches are precise microbiota editing by utilizing molecular tools and direct modulation of gut epithelial barrier function

of effects, mainly acting via G-coupled protein receptors (GPCRs). Notably, they can downregulate proinflammatory cytokine secretion and induce differentiation of naïve T cell into T regulatory cells.<sup>9</sup> The three major pathways of dietary tryptophan metabolism leading to serotonin, kynurenine, and indole derivatives are directly or indirectly governed by the gut microbiota. These metabolites have pivotal impact on immune homeostasis, epithelial function, xenobiotic metabolism, and neurobiological functions, often by acting as ligands of the aryl hydrocarbon receptor.<sup>10</sup>

Multiple well-conducted reductionist studies using animal models mechanistically elucidated the effects of specific dietary components on health outcomes mediated by microbiota.<sup>11</sup> Those studies usually investigated the effects of individual nutrients. However, this well-controlled approach does not account for the fact that those nutrients are rarely consumed in isolation. Therefore, insights gained from such studies are difficult to translate to humans. Generalized dietary guidelines have been published for well over a century to support individuals in making healthier dietary choices. A plethora of related publications recorded often inconclusive or contradictory findings, and the lack of efficacy of generalized dietary recommendations is blatantly evidenced by the stark rise of diet-related disorders such as the metabolic syndrome. The failure to identify beneficial diets may be explained by the unjustified assumption of uniform responses to foods among individuals and neglect of factors predicting inter-individual variability. Such predictors include various lifestyle, biometric, genetic, epigenetic, and, importantly, microbiome parameters.<sup>7</sup> There is growing interest in microbiota-targeted diets. For example, there is evidence that, similar to the low-FODMAPs diet, the so-called "specific carbohydrate diet" (SCD) benefits clinical and mucosal healing in pediatric patients with inflammatory bowel disease (IBD).<sup>12</sup> A recent randomized clinical trial (RCT) in malnourished children introduced a microbiota-directed complementary food diet targeting weaning-phase bacterial taxa underrepresented in malnourished infants. This diet improved plasma biomarkers and mediators of growth, bone formation, neurodevelopment, and immune function.<sup>13</sup> Another recent RCT demonstrated that dietary fiber alleviates type 2 diabetes by promoting SCFA producing enteric commensals.<sup>14</sup> However, the conceptual premises of many of those dietary approaches are rooted in old-school paradigms and fall short of accounting for the many gaps in the current understanding of diet-microbiome-host interactions.<sup>11</sup> Novel microbiota-targeted diets may emerge, serving as precision tools to prevent or treat metabolic, inflammatory, and malignant diseases. Future studies on microbiota-directed diets must focus on their long-term impacts and safety and should thoroughly incorporate personalized aspects.

### 3 | FECAL MICROBIOTA TRANSPLANTATION

The concept of fecal microbiota transplantation (FMT) originated in traditional Chinese medicine and has been rediscovered by modern

medicine in the 20th century.<sup>15</sup> FMT aims at restoring a healthy fecal microbiota composition. It is now widely performed as a treatment for *Clostridioides difficile* infection (CDI), particularly for recurrent CDI.<sup>16</sup> This approach was greatly promoted by a landmark RCT where duodenal infusion of healthy donor feces was superior to standard oral vancomycin treatment with or without macrogol bowel lavage.<sup>17</sup> Now several RCTs evaluated the effect of FMT for recurrent CDI. However, all of them have significant limitations and, therefore, the US Food and Drug Administration (FDA) did not approve FMT for CDI.<sup>18</sup> Thus, FMT is currently reserved for patients with recurrent CDI who have failed appropriate antibiotic treatment. There is no consensus on the optimal fecal preprocessing and administration technique. Moreover, the long-term safety of FMT is yet to be fully evaluated. The risk of transmission of infectious diseases is explicit, and recently a MedWatch alert was announced after two patients acquired infections with multidrug resistant *Escherichia coli* from a stool donor with one fatal outcome.<sup>19</sup> Furthermore, the risk of precipitating additional noninfectious diseases by FMT cannot be fully appreciated at the moment.<sup>16</sup> The best evidence for the efficacy of FMT, beyond recurrent CDI, is provided by 4 RCTs on the IBD ulcerative colitis (UC), of which 3 reported positive outcomes.<sup>15</sup> Moreover, encouraging results were also reported from RCTs in patients with irritable bowel syndrome, chronic constipation, metabolic syndrome, colonization by antibiotic-resistant bacteria, and hepatic encephalopathy.<sup>20</sup> In allogenic hematopoietic stem cell transplantation (allo-HSCT) antibiotic treatment is essential but may subsequently impair microbial colonization resistance and thus increase susceptibility to infections. Pretreatment fecal sample banking and posttreatment FMT may be a proper means to reconstitute the posttreatment gut microbiota and thereby reduce infectious complications and improve outcomes of allo-HSCT patients.<sup>21</sup> Further RCTs are underway to evaluate the effects of FMT in nonintestinal inflammatory disorders, such as psoriasis, neurological diseases, including Parkinson's disease and multiple sclerosis, and cancers (in combination with immuno- or chemotherapy).<sup>15</sup>

All indications of FMT to date face basic questions such as appropriate patient and donor selection, optimal pretreatment regimens, administration technique, and treatment duration. And, importantly, are live microorganisms even required to achieve therapeutic efficacy? In a preliminary trial, sterile fecal filtrate alone was sufficient to restore normal bowel habits in 5 patients with CDI.<sup>22</sup> This indicates that microbial compounds, metabolites, or bacteriophages (discussed later) rather than living microorganism may mediate the therapeutic effects of FMT. This highlights that the factors mediating the efficacy of FMT need to be better characterized mechanistically. FMT may eventually be replaced by precision editing of the microbiota or targeted supply of small microbial molecules, which may represent more efficient and safer therapeutic options. Recently, a small open-label study was conducted using vaginal microbiota transplantation (VMT) from healthy donors to patients with intractable symptomatic vaginosis. VMT relieved symptoms in majority of patients and showed no

adverse events.<sup>23</sup> This exploratory study highlights that microbiota transplantation could be a useful concept applied to other commensal communities beyond the gut microbiota.

## 4 | PRE- AND PROBIOTICS

“Probiotics” are defined as live microorganisms which upon adequate administration may result in a health benefit to the host, whereas “prebiotics” are defined as substrates selectively fostering microorganisms conferring a health benefit.<sup>24</sup> Since the introduction of the concept of probiotics more than 100 years ago, a large body of research has yielded mixed results. Nevertheless, convincing evidence of clinical efficiency exists for some probiotic applications. In theory, probiotic strains may have an impact on the gut microbiome through both competitive and cooperative interactions, including competition for nutrients and biological niches, antagonism, cross-feeding and promotion of microbiota stability.<sup>24</sup> The probiotic *E coli* Nissle 1917 (EcN) has shown clinical efficacy and safety in maintaining remission equivalent to the standard mesalazine in patients suffering from UC, a disease characterized by enteric dysbiosis.<sup>25</sup> EcN is therefore approved as a treatment for UC in many countries. EcN produces microcins that can act as narrow-spectrum therapeutics by limiting the bloom of niche-competing pathogenic *Enterobacteriaceae* in the inflamed intestine.<sup>26</sup> However, probiotics yielded disappointing results in the other major form of IBD, Crohn's disease (CD).<sup>27</sup> The lack of response in CD is obviously not attributable to a lower relevance of intestinal dysbiosis. More recently, a RCT utilizing a synbiotic (combination of pre- and probiotic) containing *Lactobacillus plantarum* ATCC-202195 showed promising results in preventing sepsis in a cohort of >4500 infants from India.<sup>28</sup> In contrast, a multicenter, randomized controlled phase 3 study failed to demonstrate any benefit by the probiotic strain *Bifidobacterium breve* BBG-001 in preventing necrotizing enterocolitis or sepsis in preterm infants.<sup>29</sup> Translational hurdles may hamper successful clinical implementation of probiotics, such as in the case of *Lactobacillus rhamnosus* JB-1, which failed to confer mental health benefits to patients despite promising results in preclinical models.<sup>30</sup> Moreover, potentially harmful consequences of probiotics need to be considered. Administration of a widely available over-the-counter probiotic containing different bifidobacterial and lactobacilli strains resulted in impairment rather than promotion of postantibiotic gut microbiota recovery in both humans and mice.<sup>31</sup>

These results highlight that any trial design utilizing probiotics needs to take carefully into account inherent differences between probiotic strains and the pathophysiology underlying the targeted disease. An additional layer of complexity is added by the recent finding that probiotic mucosal colonization patterns and associated enteric transcriptional responses are personalized, depending on various host features including the individual pretreatment microbiome composition.<sup>32</sup> This underscores the need for studies complementing existing empiric probiotics treatments by personalized probiotic approaches. Targeted supplementation of gut microbiota

community members deficient in diseased states has potential as an innovative probiotic strategy. For example, supplementation of *Akkermansia muciniphila*, a commensal deficient in obesity, may reduce body weight and improve metabolic parameters in obese individuals.<sup>33</sup> Novel experimental probiotic therapies are emerging using newly constructed recombinant strains and promising novel microbial species but await testing in vivo.<sup>24</sup>

## 5 | POSTBIOTICS

The gut microbiota produces a myriad of unique small metabolites that interact with the host locally or systemically upon accumulation in the serum. “Postbiotics” are defined as microbe-derived bioactive compounds that may confer a health benefit.<sup>34</sup> They represent a potential “shortcut” to achieve a therapeutic effect while circumventing the technical challenge to seed live microbes that produce them. As engraftment of probiotic strains or successful utilization of prebiotics may depend on the individual gut microbiome composition,<sup>32</sup> these interindividual differences may render the health effects of pre- and probiotics unpredictable. In this light, bacterial metabolites may represent a more controlled, reproducible and reliable therapeutic strategy. Moreover, they may ease storage, delivery, and application.<sup>34</sup>

Supplementation of SCFA was successfully applied to ameliorate colitis in a mouse model through acting on the receptor GPR43.<sup>35</sup> In a recent study using a mouse model of amyotrophic lateral sclerosis (ALS), a detrimental neurodegenerative disease, ALS-prone mice showed a reduced abundance of *A muciniphila*. Systemic delivery of nicotinamide, a metabolite produced by *A muciniphila*, through osmotic pumps ameliorated neurological symptoms.<sup>36</sup> The class of GPCRs constitutes a significant part of druggable receptor targets.<sup>37</sup> In a recent publication, the authors implemented a high-throughput screening method harnessing the entire human nonolfactory “GPCRome” as a lens to detect multiple novel interactions between host GPCRs and microbiome-derived metabolites.<sup>38</sup> The feasibility of such an orthogonal approach for parsing the microbial metabolome may greatly promote postbiotic drug discovery. Further studies are warranted to establish the therapeutic efficacy and safety of microbiome-derived metabolites in humans.

## 6 | BACTERIOPHAGES

(Bacterio-)phages are small viruses infecting and replicating within bacteria and represent the most ubiquitous and diverse entities in the biosphere.<sup>39</sup> After their discovery in the early 1900s, phages were the primary therapy against bacterial infections for almost 25 years before being replaced by antibiotics in the 1940s. However, they remained a popular treatment in some Eastern European countries.<sup>40</sup>

The major advantage of antibiotics is their broad-spectrum action against multiple infectious agents, which allows for fast therapy initiation before definite identification and susceptibility

testing of the underlying infectious agent. However, as a drawback of this broad efficacy, antibiotics destroy the commensal microbiota and exhibit selection-pressure toward antibiotic-resistant pathogen strains. In contrast, phages are very specific to their bacterial host and, therefore, are increasingly endorsed as a potential antibacterial alternative in the era of rising global antibiotic resistance.<sup>40</sup> Recently, an RCT reported successful treatment of wound infections with *Pseudomonas aeruginosa* using a phage “cocktail.”<sup>41</sup> In addition to general dysbiosis, specified “pathobionts” may drive pathology in noninfectious inflammatory diseases. Notable examples are pathogenic strains of *E coli* in IBD.<sup>42</sup> Phages have the potential for targeted elimination of pathobionts to improve disease outcomes. Currently, phage therapy faces many challenges, including very narrow host range (up to the strain level), their unpredictable long-term effect on host and microbiota, unclear phage selection criteria, and lack of well-curated public phage databases.<sup>40</sup> Emerging approaches utilizing engineered phages may help to overcome those hurdles.

Phages and other viruses are an integral part of the human microbiome (“virome”). Emerging evidence points toward the physiological significance of trans-kingdom-interactions and altered enteric virome ecology in human diseases such as type 1 and type 2 diabetes, IBD, or cancers.<sup>43</sup> Evidence for participation of the virome in disease-associated dysbiosis points toward a possible role of commensal phages in maintaining microbiota homeostasis or promoting pathology. This may pave the way for harnessing of phages to restore homeostatic microbiota composition. However, the study of the virome in diseased states is currently constrained by technical limitations. Importantly, up to 90% of sequences encountered in human viromes currently cannot be annotated (so called viral “dark matter”). Nevertheless, technological progress in wet-lab and computational routines can be expected in this field.<sup>43</sup>

## 7 | OTHER STRATEGIES

In addition to the previously discussed approaches, new microbiota-targeted treatments are emerging. The engraftment of probiotics strains of exogenously supplied commensals is volatile. Recently, the feasibility of finely tuned control of the abundance of specific strains has been demonstrated. The authors achieved this by introducing a *Bacteroides* strain harboring a rare gene cluster for the utilization of the marine polysaccharide porphyran. Porphyran administration to the murine host created an exclusive metabolic niche that enabled finely tuned control of the abundance of the respective strain.<sup>44</sup>

Inflammatory diseases of the gastrointestinal tract are often characterized by bloom of the facultative anaerobic family *Enterobacteriaceae*. This bloom is facilitated by bacterial molybdenum-cofactor-dependent anaerobic respiratory enzymes. Tungsten can replace molybdenum in the molybdopterin cofactor, rendering it inactive. In a mouse model of colitis, treatment with tungsten-induced targeted depletion of *Enterobacteriaceae* and

ameliorated colitis.<sup>45</sup> This demonstrates that such as simple natural compound can be utilized for therapeutic precision editing of the microbiota.

Many inflammatory diseases are characterized by perturbed host intestinal barrier function. The intestinal barrier is a complex multilayered structure regulated by biophysical factors such as osmotic pressure, microbiota-derived molecules, and host-derived mediators. Strategies aiming at directly restoring epithelial barrier function, such as administration of indole or related metabolites, is a comparatively unexplored exciting new avenue of research.

## 8 | ROLE OF THE GUT MICROBIOTA IN TRANSPLANTATION

Despite the remarkable progress achieved in organ transplantation, complications due to infection and rejection frequently undermine its long-term benefits. Emerging evidence points toward microbiota as an important player affecting transplantation outcomes. In transplant recipients dysbiosis is frequently observed.<sup>46</sup> This typically includes reduced biodiversity and a bloom of various Proteobacteria, *Enterococcus* or *Streptococcus*.<sup>47</sup> However, the study of the role of microbiota in transplant recipients is still in its infancy and faces a particular challenge in putative contributions of both recipient and donor microbiota. Interestingly, the transplantation of colonized in contrast to widely sterile organs is associated with increased rejection rates. An intact whole-body microbiota can accelerate organ rejection by promoting activation of graft-reactive T cells by antigen-presenting cells (APCs).<sup>48</sup> In a study using allo-skin transplantation in mice, a single commensal, *Staphylococcus epidermidis*, was sufficient to drive rejection by augmenting the ability of skin APCs to promote differentiation of alloreactive T cells.<sup>49</sup> Gut microbiota-dependent immune modulation predicts outcomes of cardiac transplantation in mice through stimulation of myeloid cells and changes in both lymph node architecture and permissiveness. In the same study, the transfer of the commensal *Bifidobacterium pseudolongum* alone was sufficient to reduce cardiac graft inflammation and fibrosis.<sup>50</sup> The potential of adjuvant approaches combining standard immunosuppression with microbiota-targeted interventions was exemplified by an animal study, where the combination of the tacrolimus with FMT resulted in increased skin allograft survival.<sup>51</sup>

Increasingly, potent immunosuppressive medications have reduced the rejection rate, which, however, comes at a trade-off of increased susceptibility to opportunistic infections.<sup>52</sup> Gut microbial perturbations associated with allo-HSCT or liver transplantation give permission to colonization with multidrug-resistant bacteria,<sup>53</sup> predispose to bacteremia,<sup>47</sup> and lead to decline of butyrate-producing taxa and consecutively decreased resistance toward viral respiratory infections.<sup>54</sup>

Together these results highlight the need for therapeutic approaches addressing posttransplant microbiome health in order to reduce the rejection and infection burden in transplant recipients.

## 9 | CONCLUSIONS

In the last decade, remarkable progress has been achieved in the field of microbiome research. These advances are promoting innovative microbiome-targeted precision therapies. However, in order to establish microbiota-targeted treatments in clinical routine, many conceptual pitfalls and translational hurdles are yet to be overcome. Until recently, clinical management in transplantation medicine followed a "one size fits all" approach. The evolution of "omics" tools, including microbiome techniques, advances the field toward personalized medicine. Progress in understanding of the microbiome's interplay with effector immunity may help to design new strategies to improve transplantation outcomes. Immunomodulation through microbiota-manipulation may become a powerful tool to improve graft acceptance and survival. Moreover, frequent concomitant problems in transplant recipients such as malnutrition or colonization and infections with antibiotic-resistant pathogens could be addressed by future microbiota-targeted treatments. Standardized, rigorous, and unbiased preclinical and clinical studies, similar to preceding successful human interventions, are required to introduce microbiota-targeted therapies into transplantation medicine.

### DISCLOSURE

The authors have conflicts to disclose as defined by the *American Journal of Transplantation*. EE is a consultant at Daytwo and BiomX.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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**How to cite this article:** Liwinski T, Elinav E. Harnessing the microbiota for therapeutic purposes. *Am J Transplant*. 2020;20:1482-1488. <https://doi.org/10.1111/ajt.15753>