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MICROBIOTA AND FAECAL MICROBIOTA TRANSPLANT

B.H. Mullish[1,2], J.L. Alexander[1,2], J.P. Segal[1,3]

[1]Division of Digestive Diseases, Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, United Kingdom
[2]Departments of Gastroenterology and Hepatology, Imperial College Healthcare NHS Trust, London, United Kingdom
[3]Department of Gastroenterology, Hillingdon Hospital, The Hillingdon Hospitals NHS Foundation Trust, Uxbridge, United Kingdom

Corresponding Author: James L. Alexander, MD; email: j.alexander@imperial.ac.uk

Abstract: As the range of disease states associated with the gut microbiome expands – and the mechanistic links between the gut microbiome and host physiology further deepens – so interest also grows in microbiome manipulation as medical therapy. In particular, bolstered by its established role in recurrent *C. difficile* infection (and promising results in other conditions), faecal microbiota transplant (FMT) has remained of growing global focus. This article reviews the key FMT-based studies published between April 2020-March 2021. While the COVID-19 pandemic was the dominant challenge of the year, important FMT trials of interest were published for patients with a range of different conditions. The emergence of 'next generation' microbiome therapeutics offers an additional perspective and new opportunities within the field.

Keywords: Gut microbiome, Faecal microbiota transplant, Antibiotic resistance, Clostridioides difficile infection, Inflammatory bowel disease, Irritable bowel syndrome, Obesity, Immune checkpoint inhibitors.

FMT AND *CLOSTRIDIOIDES DIFFICILE* INFECTION

FMT for recurrent/refractory *C. difficile* infection (CDI) remains the indication with the strongest clinical basis, and it has continued to be an active area for ongoing research during this period. Some of the most significant recent developments in this field are summarised within Table I.

FMT DONOR SCREENING, AND RISK OF INFECTION TRANSMISSION

As with all aspects of healthcare, the COVID-19 pandemic was the major development of the year and presented obstacles to many aspects of the FMT pathway[1]. International networks of FMT experts rapidly responded by refining best practice donor screening pathways, initially recommending enhanced donor questionnaires, SARS-CoV-2 donor nasal swabbing and extended stool quarantine[2]. After the subsequent recognition of the potential for prolonged SARS-CoV-2 shedding within stool[3], the importance of faecal testing for SARS-CoV-2 as a component of donor screening was recognised[4]; assays were rapidly developed[5,6], refined[7,8], and put into practice. As the pandemic evolves, so do the areas of focus as they apply to FMT, with implications of donor SARS-CoV-2 vaccination being an area of more recent interest[9].

TABLE 1. SUMMARY OF RECENT KEY DEVELOPMENTS IN THE FIELD OF FMT OF *C. DIFFICILE* INFECTION.

Topic:	Findings:
Updated efficacy data	• The initial report of the North American FMT National Registry provided data on 259 CDI patients receiving therapy. CDI remission was achieved by 200/222 patients by one-month post-FMT, with the majority receiving only one FMT. FMT was safe and well tolerated[56]. • In an updated systematic review and meta-analysis of studies using FMT for recurrent CDI, the overall remission rate at week 8 following repeat FMT (24 studies, 1855 patients) was 91% (95% CI: 89-94%, I^2=53%), and 84% (80-88%, I^2=86%) following single FMT (43 studies, 2937 patients)[57]. In comparison with vancomycin, the number needed to treat (NNT) for repeat FMT was 1·5 (1·3–1·9, p<0·001) and 2.9 (1·5-37·1, p=0·03) for single FMT.
Impact of FMT upon mortality from severe and fulminant CDI	• A large retrospective analysis of CDI outcomes before and after implementation of an inpatient FMT programme for severe and fulminant CDI demonstrated marked reductions in need for colectomy and mortality after FMT became available[58].
FMT for recurrent CDI in patients with co-existing IBD	• In a prospective study of FMT for the treatment of recurrent CDI in 49 patients with underlying IBD, CDI remission was achieved in 44 patients[59]. Four of the FMT non-responders received a second FMT and entered remission from CDI after this. • Further analysis of this study demonstrated low levels of worsening of IBD in association with FMT, with only one patient developing a UC flare[60]. Restoration of the gut microbiome and metabonome after FMT was comparable to that observed after FMT for recurrent CDI in patients without IBD.
Mechanisms of FMT in treating recurrent CDI	• Successful FMT in patients with recurrent CDI not only restores bile acid and short chain fatty acid microbiome functionality, but also restores other microbially-derived small molecules, including trimethylamine[61]. • Successful FMT for recurrent CDI was associated with a shift in secretory immunoglobulin A intestinal microbiota targeting to resemble that of the healthy stool donor[62]. FMT in patients with recurrent CDI also results in restoration of Th17 cells specific for the *C. difficile* TcdB toxin, as well as significant increases in anti-TcdA and anti-TcdB IgA and IgG[63]. • In a mouse model of CDI, the presence of $CD4^+$ $Foxp3^+$ T-regulatory cells was demonstrated to be necessary for FMT to induce CDI remission[64].
Approaches towards 'next generation' FMT products for CDI	• An oral encapsulated formulation of 40 lyophilised bacterial species, initially isolated from stool of a healthy donor ('MET-2'), induced remission after up to two treatments in 95% (18 out of 19) patients with recurrent CDI[65]. • RBX7455 – a room temperature stable, orally administered microbiome product derived from the stool of a single healthy stool donor – was also highly-effective at inducing remission from recurrent CDI[66]. • Both products were safe and well-tolerated.

While the scale of the COVID-19 challenge remains daunting, the pandemic has demonstrated that the collaborative international networks of FMT specialists that have become established are able to collaborate, share best practice and adapt effectively at speed, reinforcing their clear value.

Optimal donor screening for FMT remained an area of ongoing debate and evolution throughout the year[10]. This topic has attracted particular interest from clinicians and regulators alike since a 2019 report of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* being transmitted from donor to two immunocompromised FMT recipients; both developed bacteraemia, and one died[11]. Screening for ESBL in the donor had not been performed prior to the FMT and was only recognised on post-hoc 'look back'[11]. More recently, a study from OpenBiome reported seven FMT recipients experiencing adverse events after transmission of Shiga toxin-producing *E. coli* (STEC) from FMT, which was prepared from the same donor[12]. Two patients this year were also reported to have acquired enteropathogenic *E. coli* (EPEC) *via* FMT, with one requiring hospitalisation[13]. As a result of these events, the United States Food and Drug Administration (US FDA) recommended that all donor stools be screened for STEC and EPEC *via* nucleic acid amplification tests[13].

FMT AND INFECTION

Increasing global rates of antimicrobial resistance has been a major drive for research into novel therapeutic approaches. Recognition that the intestinal microbiome is the principal reservoir for multi-drug resistant organisms (MDROs) – coupled with the recognition that the MDRO-colonised gut appears similar ecologically to that of the colon in CDI – has promoted interest in FMT as a potential tool for intestinal decolonisation of MDROs. In one study of 15 patients colonised with carbapenemase-producing *Enterobacteriaceae*, treated with capsulised FMT, nine had undergone intestinal decolonisation by one month[14]. Conversely, in an observational study of 20 patients colonised with a range of MDROs – including patients with haematological malignancy undergoing haematopoietic cell transplant, renal transplant recipients, and patients with recurrent urinary tract infections – only 7/17 with full follow-up decolonised after upper gastrointestinal (GI) FMT, which is comparable to the recorded rates of spontaneous MDRO decolonisation[15]. However, of particular interest, it was noted that even despite modest decolonisation rates, treated patients had marked clinical benefits, including fewer bacteraemias (both MDRO-related and all cause), reduced length of hospital stay, and a lower requirement for carbapenems. In this latter study, it was noted that decolonisation was assessed *via* highly sensitive PCR assays, and it is possible that stool MDRO titres were reduced even if true total decolonisation did not occur[16].

FMT AND GASTROINTESTINAL DISEASE

Pouchitis

The mainstay of treatment for pouchitis remains antibiotic therapy, reflecting an apparent key contribution of the gut microbiome to the condition. By extension, a potential role for microbiome therapies – including FMT – has been of interest. To date, most FMT trials for pouchitis have given disappointing results[17]. In a further randomised study, 26 patients with chronic pouchitis were randomised to receive either donor FMT or autologous FMT[18]. Patients received two FMTs into the pouch at week 0 and 4 and were followed-up for 52 weeks. Relapse-free survival did not differ between the two groups; in subgroup analysis, those patients using continuous antibiotics before FMT had a shortened relapse-free survival in the intervention group compared with placebo.

Inflammatory Bowel Disease

While there have been no new randomised clinical trials exploring the role of FMT in the treatment of ulcerative colitis (UC), analyses of samples from prior studies have given further insights into the mechanisms by which FMT may act in this setting. In particular, high levels of baseline gut *Candida* in UC patients predicted good subsequent clinical response to FMT, and reduced *Candida* post-FMT was associated with reduced disease severity[19]. The potential role for FMT has also been an area of interest in Crohn's disease[20]. Specifically, as a follow-up to their earlier clinical pilot study of FMT for Crohn's disease, Kong and colleagues performed metagenomic sequencing of samples collected pre- and post-intervention; as well as defining specific bacterial strains transferred from donor to recipient, researchers were also able to correlate engraftment of certain *Actinobacteria* with improved disease outcomes[21].

Irritable Bowel Syndrome

Prior GI infection is a frequent precursor to irritable bowel syndrome (IBS) and some studies have suggested altered patterns of faecal microbiota composition in IBS patients compared to controls. Consequently, a contribution from the gut microbiome to IBS, and – by extension – a possible role for FMT in its treatment, has been postulated[22]. Previous FMT clinical trials in IBS have shown contradictory results and, at most, a modest benefit[23]; however, interpretation of these early studies was limited both by small patient numbers and variable disease phenotype[24].

This year, two double-blinded, randomised controlled trials of FMT for IBS utilised conventional healthy donor *vs* autologous FMT designs, with one trial using nasojejunal FMT[25], and the other using colonoscopic administration[26]. The colonoscopic study noted a transient improvement in IBS symptom severity score (IBS-SSS) at three months in healthy donor recipients, but the primary end point (50 point reduction in IBS-SSS) was not met[26]. In the nasojejunal FMT study[25], by three months post-FMT, bloating and IBS-related symptoms had improved to a significantly greater degree in healthy donor *vs* autologous FMT recipients, but this symptom relief was lost as further time passed. Patients responding to an initial FMT had restored symptom relief after a second FMT, but those patients not responding to a first FMT also did not respond to a second.

In another randomised double-blind study, 165 patients were randomised in a ratio of 1:1:1 to receive placebo, or thawed FMT slurry of either 30 g FMT or 60 g FMT, via gastroscopy to the duodenum[27]. FMT was derived from a single, well-phenotyped donor, referred to by the study authors as a 'superdonor' based upon their lack of medication/ antibiotic exposure, normal range BMI, healthy lifestyle and diet, mode of birth by vaginal delivery, and high diversity stool microbiome. The primary endpoint was a 50-point reduction in IBS-SSS at three months post-FMT, and was achieved by 23.6% of placebo patients, 76.9% of 30 g FMT patients, and 89.1% of 60 g FMT patients. FMT was associated with changes in gut microbiome composition as well as levels of faecal short chain fatty acids in the treatment arms[27,28], with levels of butyrate inversely correlating with IBS symptom scores post-FMT[28]. As such, in contrast to earlier IBS FMT studies, the study authors concluded that FMT holds promise for IBS treatment, but may require careful donor selection.

FMT AND METABOLIC AND ENDOCRINE DISEASE

Obesity and metabolic syndrome have remained a key area of interest for FMT trialists. One double-blind study of FMT for obesity recruited 22 patients who were obese (BMI >35 kg/m^2; but without other features of metabolic syndrome) and randomised 1:1 to two courses of capsulised FMT or placebo[29]. FMT was all obtained from a single stool donor, with BMI 17.5 kg/m^2. Over 26 weeks of follow-up, no differences in either weight loss or glucagon-like peptide-1 levels were seen between FMT and placebo-treated patients; however, gut microbiome and bile acids were seen in FMT recipients to at least partially resemble that of donors. Furthermore, a subsequent analysis demonstrated that there was a significantly reduced change in the glucose area under the curve (AUC) at week 12 in FMT recipients compared to baseline, and reduction in the change of insulin AUC at week 6 in FMT recipients compared to baseline[30], suggestive of a subtle but significant metabolic benefit related to FMT's use.

Further insights into the potential role of gut microbiome modulation as an intervention for weight loss and dysmetabolism was provided by the DIRECT PLUS study[31]. In the first phase of the study, middle age patients who were obese (waist circumference: men >102 cm, women >88 cm) or with dyslipidaemia were assigned for six months to increase their polyphenol intake (in the form of walnuts), and to also receive either general healthy dietary advice, a Mediterranean diet, or a 'green-Mediterranean diet' (i.e., Mediterranean diet with added green tea and *Wolffia globosa,* a green flowering plant). Mean weight loss of participants was 8.3 kg, and participants provided a stool sample for processing into FMT at the end of this phase of the study. 90 study participants were then randomly assigned either to receive 100 capsules of their own stool as autologous FMT or placebo FMT over the course of the next eight months; the primary outcome was regain of the previously-lost weight. Weight gain over the month 6-14 period was similar between participants receiving either autologous FMT or placebo. However, among study participants receiving autologous FMT, those who had previously been in the green-Mediterranean category had significantly reduced weight regain compared to placebo (while no reduced weight regain was seen among those previously in the other two dietary groups). Of particular interest, the green-Mediterranean diet was the only intervention resulting in a significant change in the gut microbiome during the weight loss period. As such, this study suggests that particular targeted interventions (including high polyphenol and green plant intake) may be a targeted means to alter the gut microbiome to result in host metabolic improvements.

Two clinical studies investigating FMT as treatment for non-alcoholic fatty liver disease (NAFLD) also were published over this period. In a pilot study of 21 patients with NAFLD (who

together covered the full range of severity of the condition), six received autologous FMT, whilst 15 received healthy donor FMT, all *via* the upper GI tract[32]. While no improvements in insulin resistance or liver fat (measured via magnetic resonance) were observed, an improvement in small intestinal permeability (as measured via lactulose: mannitol test) was observed at six weeks post-FMT in the seven patients with increased gut leak at baseline. A further double-blind trial reported the outcomes of 10 NAFLD patients receiving upper GI lean vegan donor FMT (three FMTs at eight-weekly intervals), comparing them to 11 patients receiving autologous FMT as a control arm[33]. Liver biopsies were taken at the beginning and end of the study (24 weeks), and a trend towards histological improvement in liver necro-inflammatory scores was observed. Of note, recruited patients in this second study tended to have relatively early disease based on histological scoring, and participants with type 2 diabetes mellitus were excluded, which may impact upon the generalisability of results.

Recent research into the basis of type 1 diabetes mellitus (T1DM) has inferred a role for perturbed microbiota-immune interactions in pancreatic beta-cell destruction, raising interest in the possibility of microbiota restoration as a potential treatment approach. de Groot and colleagues reported a trial of autologous *vs* healthy donor FMT in patients aged 18-30 years who had been diagnosed with T1DM within the past six weeks[34]. 10 patients received three autologous FMTs over the course of four months, and 11 patients received allogenic FMTs. The primary endpoint was preservation of stimulated C peptide after mixed meal test over 12 months, and this endpoint was reached in healthy donor FMT recipients in comparison to autologous FMT recipients.

FMT, MALIGNANCY, AND ANTI-CANCER THERAPY

Immune Checkpoint Inhibitors

Immune checkpoint inhibitor (ICI) medications - targeting both the PD-1 and CTLA-4 pathways - have been one of the major therapeutic advancements in oncology of the past decade, resulting in markedly improved survival rates for a range of haematological and solid organ malignancies. However, there has been marked between-patient heterogeneity with regards to both treatment efficacy and toxicity, and modifiable factors underlying this have been an area of interest. Large cross-sectional human studies have demonstrated that the baseline gut microbiome composition predicted response to ICI therapy, and that increased baseline alpha diversity was also a predictor of ICI response[35-37]. Further analysis of human data demonstrated that antibiotic use prior to ICI instigation was closely associated with reduced progression-free survival and overall survival[36,38]. Subsequent work demonstrated that FMT into antibiotic-treated or germ-free mice of stool derived from patients non-responding to ICIs resulted in reduced PD-1 blockade and anti-tumour effect, while FMT from stool from responding patients resulted in effective tumour control[35-37]. The gut microbial metabolite inosine has recently been identified as a key microbial mediator of the efficacy of ICIs[39].

Extending upon these findings, two early studies were reported at the same time assessing the impact of FMT in patients with anti-PD-1-refractory metastatic melanoma[40,41]. The phase 1 study included 10 patients; the two stool donors used were patients previously treated with anti-PD-1 monotherapy for metastatic melanoma, and who had been in clinical remission for over one year[40]. Patients received three FMTs (one colonoscopic, two capsulised) over the course of 12 days, before re-initiation of nivolumab as anti-PD-1 therapy; six cycles of nivolumab were completed and fortnightly FMT were then received over the course of 90 days. By the end of the study, one patient had entered clinical remission, and two achieved partial responses; of interest, all three responding patients were treated with stool from the same donor. In the study from Davar et al[41], 16 patients with anti-PD-1-refractory metastatic melanoma were treated with FMT derived from seven donors (four with complete response, three with partial response). A single colonoscopic FMT was given, together with pembrolizumab at baseline and then every three weeks. Six patients reached the main endpoint of re-establishment of response to therapy and response was associated with the presence of taxa previously shown to correlate with anti-PD-1 efficacy from the families *Lachnospiraceae, Ruminococcaceae* and *Bifidobacteriaceae.* The investigators further demonstrated linkage between these microbiota,

CD8+ T cell activation and reduced expression of circulating cytokines such as IL-8, higher levels of which have been associated with worse outcomes with anti-PD1 therapy.

Tyrosine Kinase Inhibitors (TKIs)

The introduction of tyrosine kinase inhibitors has resulted in greatly extended survival for patients with metastatic renal cell carcinoma (RCC). However, almost 50% of patients may develop diarrhoea in association with TKIs, with drug dosing reduction or temporary cessation often required as a result. In light of previous data suggesting that TKI-related diarrhoea may be associated with gut microbiome perturbation, FMT may be a novel approach to resolve this. In this study, 20 patients receiving TKIs for metastatic RCC were randomised to receive either a single colonoscopic healthy donor FMT or placebo and monitored for progression of diarrhoea over eight weeks[42]. Complete resolution of diarrhoea was observed at significantly higher rates in the FMT arm than placebo for up to eight weeks (although the number of patients reporting resolution fell from 10/10 at week 1 to 3/10 at week 8).

Graft-Versus-Host Disease

Haematopoietic cell transplantation (HCT) is a key intervention in patients with haematological malignancy. However, a well-recognised potential complication of HCT is the anti-host immune responses described as graft-versus-host disease (GvHD), with those patients developing the steroid-refractory form of the condition experiencing a particularly poor prognosis. Disturbance of both gut microbiome composition (including reduction in the bacterial families *Lachnospiraceae* and *Ruminococcaceae*) and functionality (reduced gut short chain fatty acids) have both been linked to risk of GvHD in human patients[43], with the frequent courses of antibiotics and chemotherapy received by patients with haematological malignancy being a major risk factor for such microbiome changes. Restoration of bacteria able to produce a particular short chain fatty acid, butyrate, had previously been demonstrated to potentially ameliorate intestinal GvHD in a mouse model[44], with a single strain of *Bacteroides fragilis* being one bacterium demonstrated to protect gut integrity and reduce GvHD[45].

van Lier and colleagues extended upon this prior work by reporting results of the administration of healthy donor FMT into 15 patients who had received allogeneic HCT and developed either steroid-refractory or steroid-dependent FMT[46]. FMT was well-tolerated, and infections developing within the recipients over the six months of follow-up did not appear to be transmitted from the donor. 10/15 FMT recipients developed a complete clinical response within one month of FMT, without the need for further GvHD-related interventions; 6/10 of these responders were able to successfully wean immunosuppressive drug therapy. An increase in gut microbial alpha-diversity and increased abundance of butyrate-producing microbiota members was also observed. Response rate was lower – at 57% – in another cohort of 11 GvHD patients (collectively receiving 16 FMTs), but these patients were notably more medically-complex than the former group, including two patients with chronic GvHD, patients with more advanced disease, and with all included patients also having intestinal colonisation with antibiotic-resistant bacteria[47]. As well as impacting upon the gut microbiome, FMT for GvHD has also recently been shown to be associated with distinctive changes in the gut virome and mycobiome[48].

FMT AND OTHER INDICATIONS

A summary of FMT for other indications is summarised in Table II.

FMT, AND NEXT GENERATION PRODUCTS

The field of FMT – and 'microbiome therapeutics' more generally – continues to attract interest and expand. One clear example of the continued growth of interest in FMT is the ev-

TABLE 2. NOTABLE FMT STUDIES FOR OTHER INDICATIONS.

FMT indication:	Intervention:	Key findings:
Infants born by Caesarean section (CS)[67]	• 17 infants born by CS received diluted FMT. • FMT was derived from own mother's stool, collected at 3-weeks prior to delivery.	• The gut microbiome of FMT-treated CS-born infants no longer resembled that of untreated CS-born infants but showed significant similarity to that of vaginally-born infants.
Systemic sclerosis[68]	• 10 patients with systemic sclerosis were randomised to 'FMT' (using an anaerobically-cultured human intestinal microbiota preparation) or placebo. • Follow-up was for 16 weeks.	• The FMT group had decreased bloating, diarrhoea and/or faecal incontinence in 4/5, compared with 2/4 in the placebo group. • One episode of laryngospasm and one duodenal perforation occurred in placebo-treated patients during gastroscopic administration.
Small intestinal bacterial overgrowth (SIBO)[69]	• 55 patients with SIBO were randomised to capsulised FMT or placebo once a week for four weeks.	• GI symptoms were significantly improved in the FMT group compared to placebo at 6 months follow-up.
Alcohol use disorder[70]	• Recruited patients with alcohol-related cirrhosis with an AUDIT-10 score of >8. • 20 patients were randomised to FMT (derived from a donor whose stool was enriched with *Lachnospiraceae* and *Ruminococcaceae*) or placebo.	• Craving reduced significantly in 90% of FMT-treated patients vs 30% in placebo at day 15. • Improved cognition and psychosocial quality of life was also observed in the FMT group.
HIV[71]	• 30 HIV+ patients (all taking antiretroviral therapy, and with CD4/CD8 <1) were randomised to receive weekly capsulised FMT or placebo for eight weeks.	• FMT use was associated with an increase in alpha diversity, and a mild and transient engraftment with donor microbiota. • FMT use was associated with reduction in intestinal fatty acid binding protein (IFABP), a marker of gut barrier dysfunction.
Checkpoint inhibitor induced (CPI) enterocolitis[72]	• 15 patients received healthy donor FMT for CPI enterocolitis after failing immunosuppressive therapy.	• 11 patients had symptomatic improvement post FMT and there were no adverse events.

er-growing breadth of countries and regions who have reported interest in or establishment of FMT services/stool banks for the first time (including South Africa[49], Brazil[50], Romania[51] and Bulgaria[52]), hopefully translating into a larger number of patients having potential access to FMT than ever before. A further major development of interest during the year has been reports of both phase 2 trial data from Finch Therapeutics (CP101; the PRISM3 trial)[53] and phase 3 trial data from Seres (SER-109; the ECOSPOR III trial)[54] of investigational 'whole microbiome' products reaching primary endpoints in reducing CDI recurrence.

In many ways, such products represent the high point of almost a decade of very active research into FMT for CDI, at last delivering a well-defined, oral product that removes many of the most obvious drawbacks related to FMT, and which are likely to be quickly evaluated for formal licensing. Nevertheless, questions still remain, including about pricing and how widespread availability of such products will be; it is of note that most clinical trials of these products have been based within North America only before now[55]. It has also been discussed as to whether the availability of such safe and effective products may lead to the disappearance of 'true' FMT as a modality of treatment. However, it is widely accepted that CDI is the 'low hanging fruit' of microbiome therapeutics (given how effective FMT is for this indication regardless of who the donor is, how it is prepared, etc.), and the contribution of the microbiome to the other conditions discussed in this

article is much more complex than for CDI. Recognising this challenge, FMT studies have continued to grow in sophistication, in particular incorporating additional levels of mechanistic analysis beyond microbiome profiles alone (including metabolomics, proteomics, immune analysis, etc.) that were not present in earlier studies. As such, there is clearly an important role for both FMT and 'next generation products', with FMT remaining an important 'discovery tool' for exploring gut microbiome-host interactions, and findings from these studies being a launchpad towards novel, more targeted methods of microbiome manipulation in the future.

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Conflict of interest

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