Proceed with caution

The human gut microbiota is an attractive target for therapeutic interventions, but there is a long way to go in this fledgling research area.

Our increasing understanding of the diversity and complexity of the human gut microbiota has been mirrored by a growing understanding of the involvement of this unseen majority not only in human health but also in disease, including associations with obesity, diabetes and inflammatory bowel disease as well as some neurodevelopmental disorders. However, moving from correlation to causality is fully acknowledged to be a lengthy and complex process that is particularly difficult for disorders that are phenotypically and/or genetically heterogeneous. Recent progress though has led to increased discussion of the tantalizing prospect of developing microbiota-directed therapies for a variety of diseases, but how realistic a prospect is this?

One area in which therapeutic modulation of the gut microbiota has had clear success already is the use of faecal transplantation in the treatment of recurrent *Clostridium difficile* infection. Although the details of one of the first examples of the use of faecal transplants (as a treatment for pseudomembranous enterocolitis) were published more than 50 years ago[1], the results of the first randomised controlled trial were only reported in 2013 (REF. 2). This small-scale, open-label trial compared the effectiveness of vancomycin treatment plus bowel lavage then duodenal infusion of donor faeces versus vancomycin treatment plus lavage or vancomycin treatment alone, and showed that *C. difficile*-associated diarrhoea was successfully resolved in 81% of those receiving the donor faeces compared with only 31% of those receiving vancomycin alone. Although highly effective, there are still many hurdles to be overcome before faecal transplantation enters the mainstream, not least of which is what is often referred to as the 'yuck factor'. This could be tackled by the development of defined, synthetic stool preparations, as was reported in the 2013 'RePOOPulate' study[3]. Here, a defined stool substitute, comprising 33 different antibiotic-sensitive bacterial isolates cultured from the stool of a healthy human donor, was used to treat two patients with recurrent *C. difficile*-associated diarrhoea. The infection resolved in both patients, and they remained symptom-free six months later.

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Even with defined, synthetic donor material, faecal transplantation as a treatment for recalcitrant *C. difficile* infection, for all it could revolutionise the treatment for this debilitating condition, can perhaps be regarded as the low-hanging fruit as far as microbiota-targeted therapies are concerned, given the relatively straightforward nature of the disease. Targeting other disorders that have been linked to the gut microbiota is seen as a much more difficult — and hence distant — prospect. The first steps on this long road are beginning to be taken, however.

In one recent high-profile example[4], researchers reported a proof of concept study demonstrating that probiotics may be used to treat autism-spectrum disorder (ASD). This study utilised the maternal immune activation (MIA) model, in which pups born to female mice that receive immune stimulation when pregnant display three core features of autism (stereotypic or repetitive behaviour, deficits in communication and deficits in social interactions). The authors found that in addition to these core features, offspring of MIA-treated mice displayed impaired integrity of the intestinal barrier, altered intestinal cytokine profiles and dysbiosis in the gut microbiota, changes which have also been observed in some individuals with ASD. *Bacteroides fragilis* treatment of MIA-treated offspring not only ameliorated the gastrointestinal deficits and corrected the dysbiosis, it also relieved some of the ASD-type behaviours, although it is important to note that socialization was still impaired. Analysis of the serum metabolite profiles identified elevated levels of 4-ethylphenylsulphate (4EPS) in the offspring of MIA-treated mice but in mice that received *B. fragilis* treatment the levels of 4EPS returned to wild-type levels. Systemic administration of 4EPS to wild-type mice was sufficient to induce anxiety-like behaviours resembling those seen in the offspring of MIA-treated mice. Thus, in this mouse model microbiota-directed therapy appears to be a promising avenue for further investigation.

Many animal models recapitulate the pathological symptoms of a human disease or its mechanistic underpinnings but often not both, hence building on promising initial data can be challenging. It is therefore necessary to ensure that the results of such work should always be communicated to the wider public in a responsible manner.

1. Eiseman, B. *et al. Surgery* **44**, 854–859 (1958).
2. van Nood, E. *et al. N. Engl. J. Med.* **368**, 407–415 (2013).
3. Petrof, E. O. *et al. Microbiome* **1**, 3 (2013).
4. Hsiao, E. Y. *et al. Cell* **155**, 1451–1463 (2013).