Response to: 'Correspondence on 'Safety and efficacy of faecal microbiota transplantation for active peripheral psoriatic arthritis: an exploratory randomised placebo-controlled trial" by McGonagle *et al*

We thank McGonagle *et al*[1] for their insightful comments on our manuscript on faecal microbiota transplantation (FMT) in active peripheral psoriatic arthritis (PsA), known as the FLORA trial.[2] We agree that the clinical findings of this first double-blind, randomised, trial of FMT in immune-mediated arthritis warrant further investigation into the underlying biological mechanisms coupling gut composition, the intestinal barrier–microbiotal interaction, and systemic inflammation in PsA and related chronic inflammatory diseases. Indeed, evidence linking the composition of the gut microbiota and initiation/progression of immune-mediated disease is limited and is primarily derived from animal models.[3] Suggested mechanisms encompass failure to induce immunological tolerance,[4] which may direct the T cell repertoire towards a pro-inflammatory phenotype including Th17 differentiation and activation seen in PsA, loss of epithelial integrity[5] and systemic translocation due to local inflammation and/or tissue damage that may enable trafficking of both activated immune cells and antigenic material to distant sites thereby creating perpetual systemic inflammatory stimuli[6] by epitope spreading,[7] bystander activation[8] and/or molecular mimicry.[9]

Reactive arthritis (ReA) represents an arthritic disease entity within the spondyloarthritis (SpA) family that is believed to be triggered by a specific gut bacteria composition. Moreover, the heterogeneous disease manifestations of ReA such as enthesitis, uveitis and sacroiliitis have been associated with enrichment of specific bacteria.[10] Given the overlapping disease manifestations of PsA and ReA, these disease entities may likely share pathophysiological features. As McGonagle *et al* point out, FMT could transiently disturb the intestinal homeostasis and trigger a flare in disease mediated by microbial modulation of immunological pathways before later restoration of immune homeostasis. That FMT can induce systemic immunological responses such as a transient increase in C reactive protein and self-limiting fever are well-known side-effects in patients receiving FMT for *Clostridioides difficile* infection and/or chronic inflammatory bowel disease (IBD).[11] Effects of FMT could also be mediated through indirect mechanisms bolstering the effects of standard therapies, including methotrexate, which participants of the FLORA trial received throughout the trial. This latter concept is known as pharmacomicrobiomics.[12] Given that compositional and functional microbiota alterations can be partly relieved by conventional synthetic disease modifying anti rheumatic drugs (DMARDs) treatment[13] and anti-tumour necrosis alfa (TNFα) treatment in patients with SpA and rheumatoid arthritis (RA),[14 15] it would have been optimal that no participants in the FLORA trial received such treatments during the trial. However, this state was not possible due to disease severity and the relatively long follow-up (26 weeks).

In addition to the clinical objectives of the FLORA trial, we aimed to generate more knowledge of FMT-induced (1) changes in the compositional, structural and functional capacity of the intestinal microbiota and the intestinal permeability, (2) occurrence of systemic translocation of microbial products and (3) changes in levels of systemic inflammation-associated proteins in patients with PsA, and how this relate to the clinical outcome following FMT both in the short term (after 4 weeks) and in the long term (after 26 weeks). Current evidence from IBD trials indicates that both clinical, patient-related and donor-related factors may be important for the clinical outcome of FMT,[16–20] thereby leading us to conclude that FMT therapies would benefit from a personalised approach.[21] Moreover, whether a 'window of opportunity' exists relatively close to disease onset[22] or at time of disease remission within which microbiota-targeted interventions are more likely to be effective needs further investigation.

The proposed causal link between microbiota community state types and PsA, which has been proven to be the case in ReA, remains to be established. However, to investigate safety and efficacy of FMT as well as enlighten similarities and differences in microbial abnormalities and FMT effect mechanisms among patients with different types of inflammatory arthritis (PsA, ReA, RA, axial SpA, gouty arthritis), IBD and pulmonary sarcoidosis, we have now initiated a new randomised trial, the FRONT trial (NCT04924270). Here, we will investigate the clinical and biological effects of weekly upper-administered, capsule FMT in treatment naïve, newly diagnosed patients with various conditions. As advocated for by translational science, we anticipate that the combination of clinical trials and in-depth basic science of microbial and immunological responses will advance our understanding of the link between the intestinal microbiota and the disease course of PsA and related chronic inflammatory diseases.

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Correction notice This article has been corrected since it published Online First. Reference 1 has been corrected.

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