Title: Shifting the paradigm of nutritional therapy of Crohn's disease

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We would like to thank Professor Mark Beattie and Dr James Ashton for their commentary on our recent publication in the Journal[(1)]. We are pleased to hear that international experts in the management of pediatric Crohn's disease (CD), consider our research commendable and of great potential to transform the current management of the condition.

We agree with them that, intuitively, the mucosa-associated microbiome should theoretically be mechanistically more informative to the pathogenesis of CD and the mode of action of exclusive enteral nutrition (EEN), but this standing doctrine remains to be proven. This is also especially hard to achieve in a pediatric population given the need for anesthesia for endoscopies. Recent pediatric studies have demonstrated different degrees of intestinal healing after EEN but have not yet published in depth microbial analysis of the samples[(2)]. In the present study we complemented the microbial effects of EEN and CD-TREAT in fecal samples, by additionally characterizing the mucosa-associated microbiome in cecal and colonic specimens, harvested from rats with and without gut inflammation. Regardless of the presence of gut inflammation, we showed that the effects of CD-TREAT and EEN on the microbiome community structure in these tissue specimens closely mimicked those we observed in feces. Here, we provide new data which illustrate that the variation in global microbiome structure is primarily explained by the animal groups (PERMANOVA analysis, R^2= 0.49; p <0.0001) and only marginally by the site of the gastrointestinal tract (PERMANOVA analysis, R^2= 0.07; p =0.02) the samples were collected from (Figure 1).

The objective of this current body of research was to accumulate high caliber pre-clinical evidence to support a novel dietary treatment for active CD. The inclusion of the small number of

patients with active CD, on treatment with CD-TREAT, aimed to translate these pre-clinical data to early signals of clinical efficacy. Recruitment to this clinical trial is currently ongoing and with additional funding from The Leona M. and Harry B. Helmsley Charitable Trust we are now extending our study to four other centers in Scotland. In this ongoing program of research, we will explore the clinical efficacy of CD-TREAT in a much larger population of adults and children with active CD, including patients with new onset, treatment naive disease. Employing a multi-omics approach, with shotgun metagenomics, meta-transcriptomics, metabolomics and proteomics analysis we will interrogate the microbial signals of CD-TREAT in depth and compare them with those of biobanked samples from 66 children with CD, followed prospectively during their treatment with EEN https://clinicaltrials.gov/ct2/show/NCT02341248. We intend to demonstrate how microbial functional and compositional signatures, at treatment initiation and during the course of CD-TREAT and EEN predict treatment response, building upon findings from our previous hypothesis-generating and mechanistic research[3; 4; 5; 6; 7]. Most importantly, we aim to explore the extent to which the efficacy signal of CD-TREAT is related to dietary variation, inherent to the composition of CD-TREAT. This work will give a platform on which to build further dietary experiments, reintroducing components which either excluded or moderated during CD-TREAT. Whilst we share the authors' enthusiasm for personalized medicine, at present, we believe understanding how and why EEN works in more than 80% of treated patients is an equally important step. This has been the basis for our previous work and our development of CD-TREAT.

References

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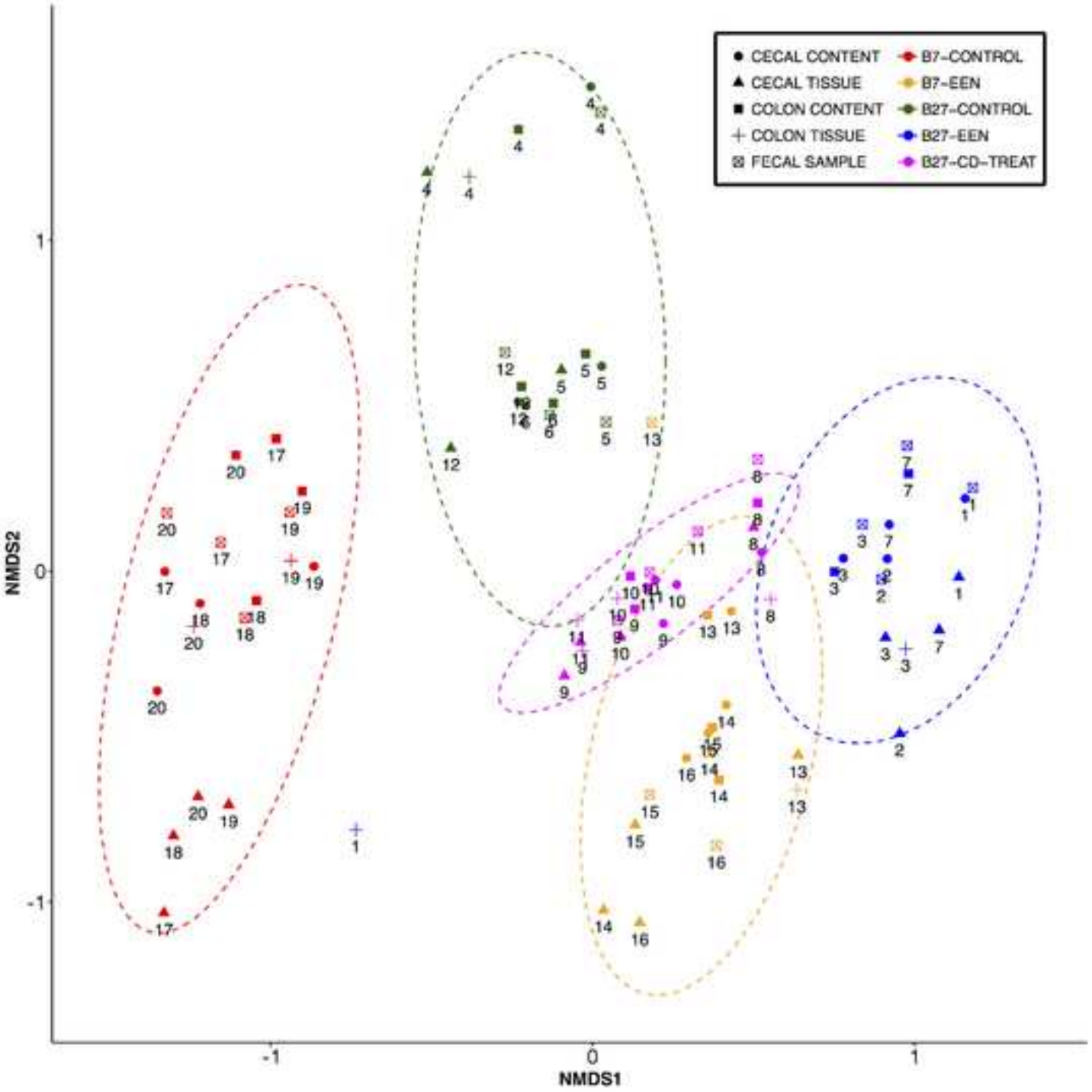
Figure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