Mechanistic understanding of 8 commensal gut bacteria associated with clinical remission in ulcerative colitis patients

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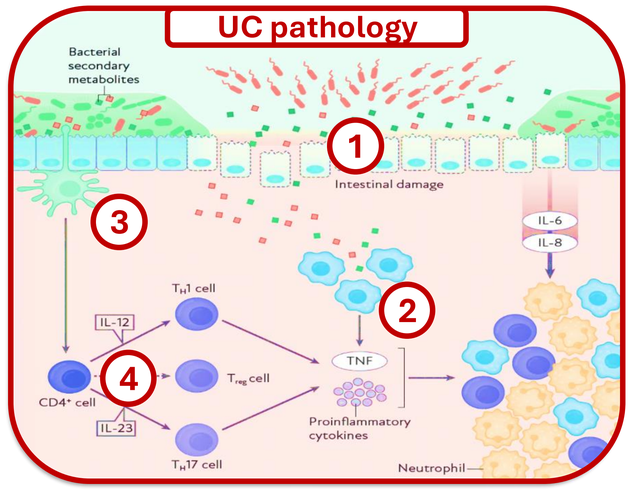
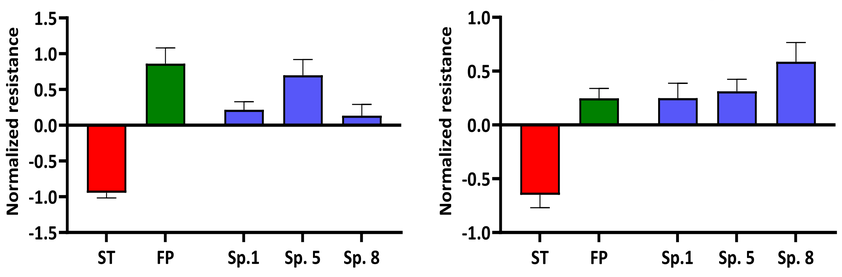
Background

- Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease characterised by damaged epithelial barrier and inflammation of the colonic lamina propria due to dysregulated innate and adaptive immune responses
- The microbiome of UC patients is altered and is thought to be a key driver of disease pathology.
- Faecal Microbiota Transplant (FMT) has been shown to be therapeutic in placebo controlled clinical trials
- Precision microbiome profiling of a human FMT study identified 8 bacterial species associated with clinical response when engrafted in mild-to-moderate Ulcerative Colitis (UC) patients
- MB310 is a Live Biotherapeutic Product for the treatment of UC comprising a strain of each of the beneficial gut commensal bacteria species and is currently in Phase 1b (COMPOSER-1 trial)
- In this work we describe how both bacteria and their metabolites were tested to understand the mechanistic drivers of these clinically beneficial species



1 ↑ Barrier Function

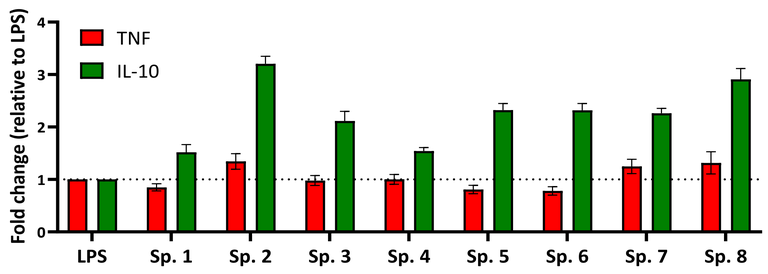


3 of the strains enhance epithelial barrier function and repair

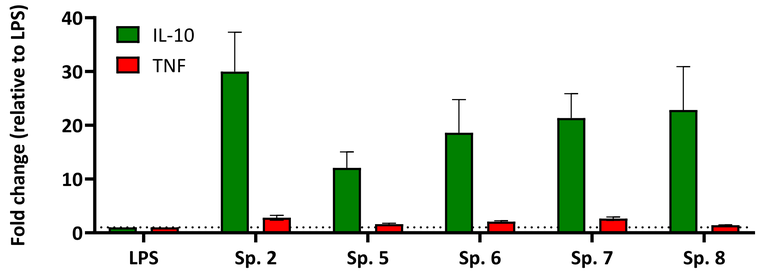
A Caco-2 monolayer was co-incubated with each strain individually for 24hr in anaerobic conditions. Barrier integrity was measured by electrical resistance across the monolayer. For barrier repair, the Caco-2 monolayer was damaged by LPS stimulation.

↑ IL-10 Production by Innate Immune Cells

2 Monocyte Derived Macrophages



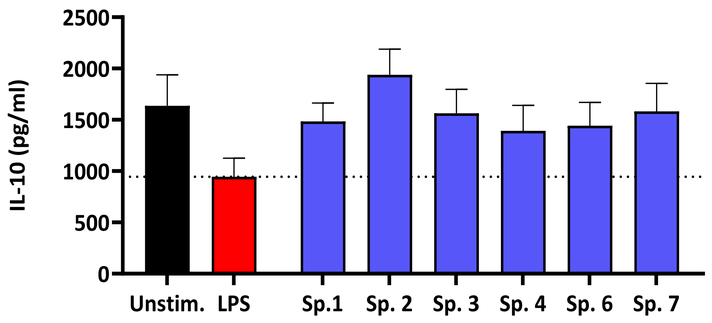
3 Monocyte Derived Dendritic Cells



Multiple strains enhance IL-10 production, but not TNF, skewing the DC and M1 macrophage responses to an immunomodulatory cytokine profile

Human monocyte derived macrophages and dendritic cells were stimulated with LPS to mimic the inflammatory environment of UC. The bacterial strains were cocultured with the cells anaerobically for 2hrs and then transferred to aerobic environment. The activation profile was determined by release of IL-10 and TNF.

↑ Regulatory T Cells by bacteria



6 strains alter DC maturation such that subsequent polarisation of CD4 T cells is skewed to increased IL-10 production

Human monocyte derived dendritic cells were matured by LPS stimulation in the presence of each strain individually. Subsequently, the DCs were co-cultured with CD4^{+ve} T cells, and T cell polarisation assessed by measuring cytokine release following restimulation

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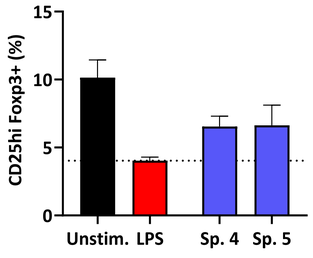
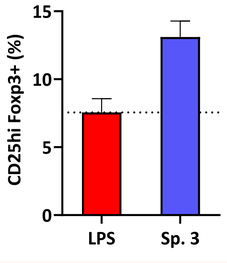
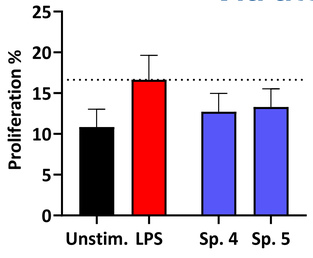




↑ Suppressive T Cells induction by bacterial metabolites

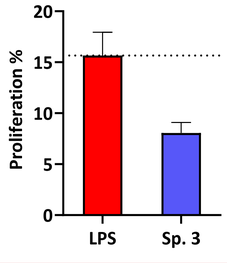
Via altered dendritic cell maturation



Metabolites from 2 strains alter DC so T cell polarisation is skewed to increased Foxp3 expression and suppressive activity

Human DCs, matured by LPS stimulation in the presence of bacterial supernatants, were co-cultured with CD4^{+ve} T cells. Treg induction was assessed by Foxp3 expression and suppressive activity by inhibition of CD4 T cell proliferation

Via altered T Cell polarisation



Metabolites from strain 3 skew T cell polarisation to increased Foxp3 expression and suppressive activity

Human DCs, matured by LPS stimulation, were co-cultured with CD4^{+ve} T cells in the presence of bacterial supernatants. Treg induction was assessed by Foxp3 expression and suppressive activity by inhibition of CD4 T cell proliferation

Conclusions

- The 8 MB310 strains, identified as being associated with clinical benefit, interact with the host in different ways to oppose key UC disease pathologies by:
  - improving gut epithelial barrier integrity and repair
  - promoting an anti-inflammatory profile of innate immune cells
  - inducing Treg cells
  - metabolites of some MB310 strains lead to induction of functionally suppressive Tregs via different mechanisms
- COMPOSER-1 is an ongoing Phase 1b trial testing MB310 in UC patients

composer[1]

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