Immunomodulatory effects of a commensal gut microbe alleviate inflammatory responses in an animal model of severe asthma through a reduction of neutrophil infiltration to the lung.

Philip Cowie, Imke Mulder*
4D Pharma PLC, UK
*Corresponding author

Background

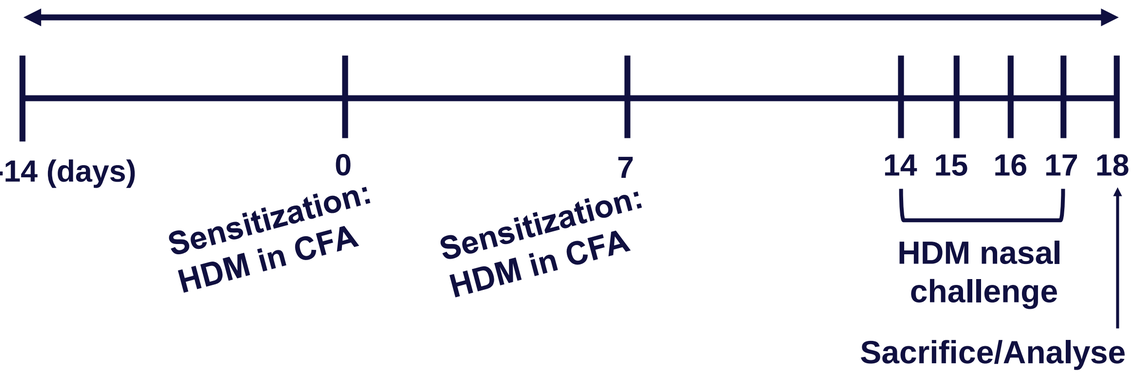
The human gut harbours ~10^{14} commensal bacteria[1] which play a critical role in mucosal immunity of the gut and at distal mucosal sites[2]. Recent evidence has demonstrated the existence of a 'gut-lung' axis with particular importance to immune responses linked to asthma. For example, supplementation of wild-type mice with a *Lactobacillus* strain reduces Th2 cytokine expression and immune cell activation reducing allergic airway responses[3]. Additionally, gastrointestinal bacterial capsular proteins can prevent asthma onset by altering T-cell activation[4]. With a view to the unmet needs of severe asthma (SA) patients we investigated the potential therapeutic effect of a commensal microbe in an animal model of severe asthma. Particular attention was paid to Th1 and Th17 cell readouts. Th1 and Th17 cells have been, separately, described as important mediators of SA; IL-17 from Th17 cells contributes to neutrophilic infiltration[5] while the Th1 canonical cytokine IFNγ contributes to airway hyperresponsiveness[6].

(1) Gill S.R. et al., (2006) Science 312, no. 5778: 1355–59; **(2)** Hooper L.V. et al., (2012) *Science* 336, no. 6086: 1268–73; **(3)** Fujimura K.E. et al., (2014) PNAS 111, no. 2: 805–10; **(4)** Johnson J.L. et al., (2015) *Glycobiology* 25, no. 4: 368–75; **(5)** Roussel L. et al., (2010) *J. Immunol.* 184, no. 8: 4531–37; **(6)** Raundhal M. et al., (2015) *JCI* 125, no. 8: 3037–50.

About 4D Pharma PLC

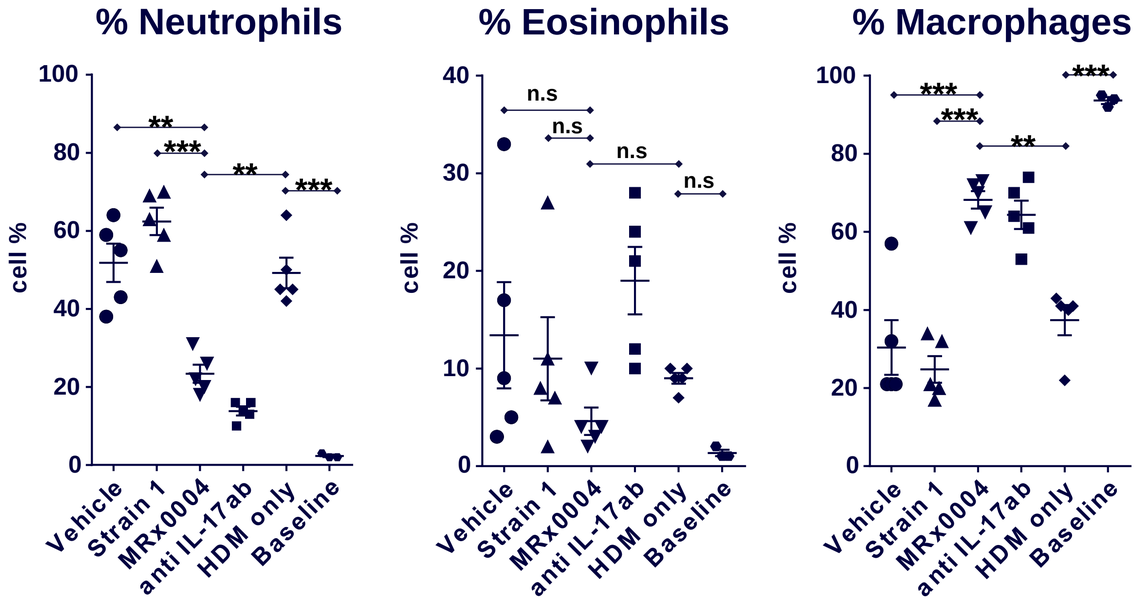
4D Pharma PLC is a pharmaceutical company focused on developing therapeutics from the human gut microbiome. Live biotherapeutic products (LBPs) derived from the gut microbiome represent a new class of drugs that contain live organisms for the prevention, treatment or cure of disease. 4D Pharma is a world leader in the LBP field and currently has two clinical stage programmes (in IBS and IBD) and a strong pipeline of pre-clinical programmes in autoimmunity, inflammation, oncology and CNS disease.

Study design



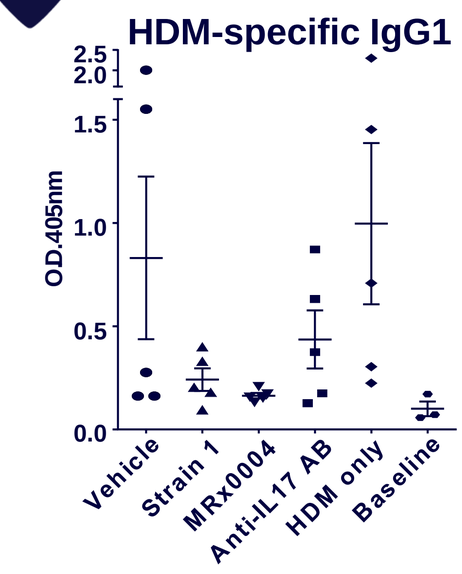
Preclinical model of severe asthma delivers a disease phenotype which is insensitive to inhaled steroids, with neutrophilic and some eosinophilic infiltration, lung histopathology and a mixed Th1/Th17 cytokine profile. 5 animals/group (3 for baseline), HDM = house dust mite, CFA = complete Freund's adjuvant, stats = ANOVA followed by Tukey's post test.

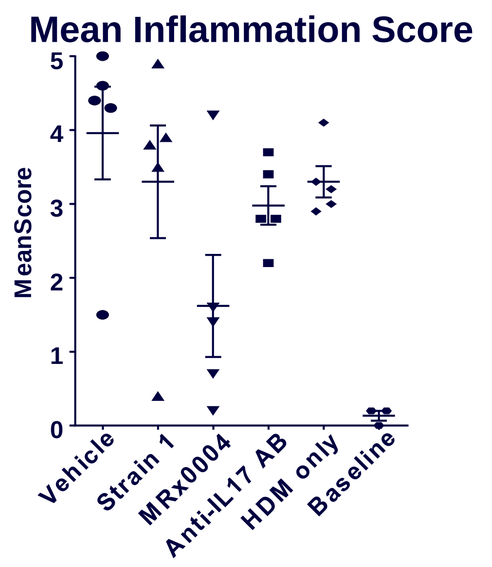
Results 1



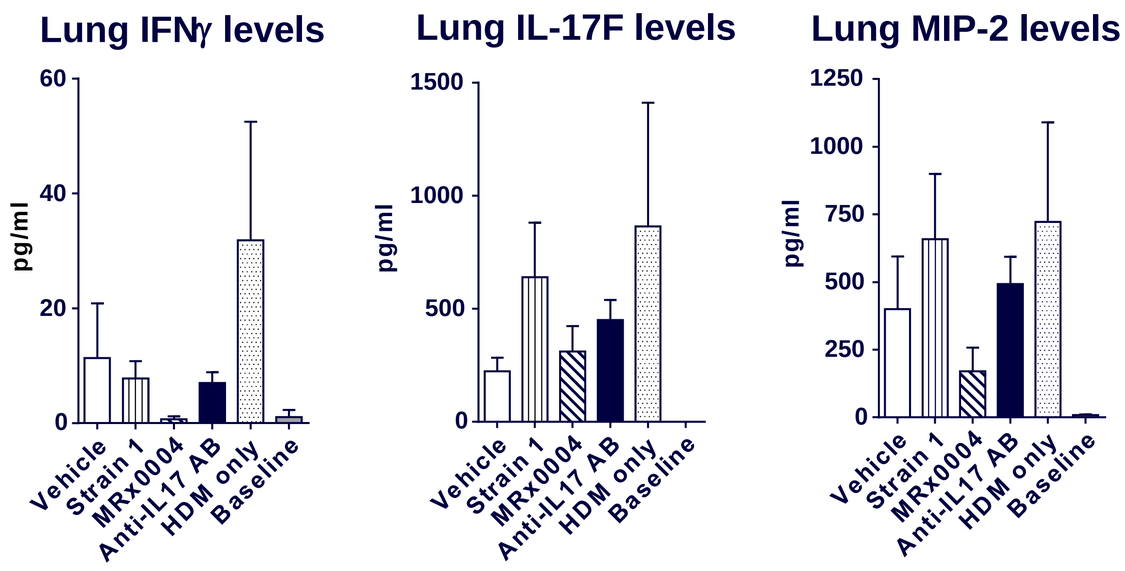
- MRx0004 shows species and strain specific reduction of neutrophil infiltration and moderate eosinophil infiltration reduction
- MRx0004 elevates macrophage levels towards baseline (wild-type)
- MRx0004 shows similar efficacy to anti-IL-17 Ab treatment at reducing neutrophilia without inducing the infiltration of eosinophils frequently observed as an undesirable side effect

Results 2





- MRx0004 consistently reduces serum HDM-specific IgG1 towards baseline levels
- Indicative of lower B cell activity and a reduced immune response
- MRx0004 has a variable effect on histopathology of lung tissue
- A trend towards reduced pathology exists which appears to be MRx0004-specific



- Reduced levels of IFNγ by MRx0004 suggests a reduction in Th1-type immune responses which are elevated in the SA model
- IL-17F levels can be reduced by MRx0004 potentially reducing host pro-inflammatory responses and neutrophil recruitment
- MRx0004-specific reduction of MIP-2 (CXCL2) is observed; a putative contributor to the reduction of neutrophils found in BAL fluid

Conclusions

- MRx0004 significantly decreases neutrophil infiltration to the lung without simultaneous induction of eosinophil infiltration; indicating therapeutic value for the treatment of SA
- Further mechanistic studies are underway to clarify the effect of MRx0004 on host immunity and identify the mediators of MRx0004's effect on the gut-lung axis
- A first-in-man clinical trial is planned for 2017 in severe asthma patients with neutrophilic and/or eosinophilic phenotype