**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 which play a critical role in mucosal immunity of the gut and at distal mucosal sites. 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. Additionally, gastrointestinal bacterial capsular proteins can prevent asthma onset by altering T-cell activation. 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 while the Th1 canonical cytokine IFN-γ contributes to airway hyperresponsiveness.

**Study design**

Daily oral dosing with vehicle or bacteria inoculum

- **Sensitization:** HDM in CFA
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- **HDM nasal challenge**
- **Lung IFN-γ levels**
- **Lung IL-17F levels**
- **Lung MIP-2 levels**

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**

- Reduced levels of IFN-γ 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

**Results 2**

- MRx0004 has a variable effect on histopathology of lung tissue
- A trend towards reduced pathology exists which appears to be MRx0004-specific

**Conclusions**

- 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

**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.

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(3) Fujimura K.D. et. al., (2014) PNAS 111, no. 5: 1805–10  

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