Bifidobacterium breve MRx-4DP0004 protects against airway inflammation in a severe asthma model by suppressing both neutrophil and eosinophil lung infiltration

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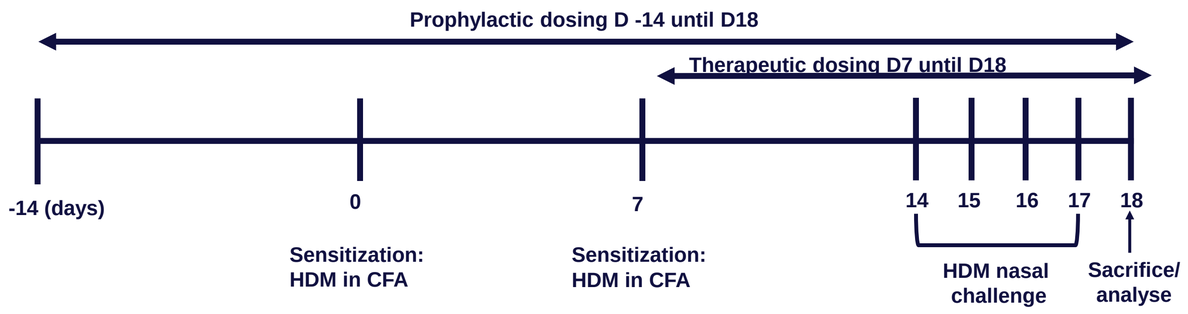
Background

- Asthma is a phenotypically heterogeneous disease characterized by recurrent, reversible airway obstruction and increased bronchial hyper-responsiveness.
- In severe asthma (SA), airway inflammation can be predominantly eosinophilic, neutrophilic, or mixed. Only a limited number of drug candidates are in development to address this unmet clinical need.
- MRx-4DP0004 is a commensal *Bifidobacterium breve* strain isolated from the microbiome of a healthy human infant.
- The strain was tested prophylactically and therapeutically by oral gavage in a house dust mite mouse model of severe asthma (Raftis *et al.*, 2018).

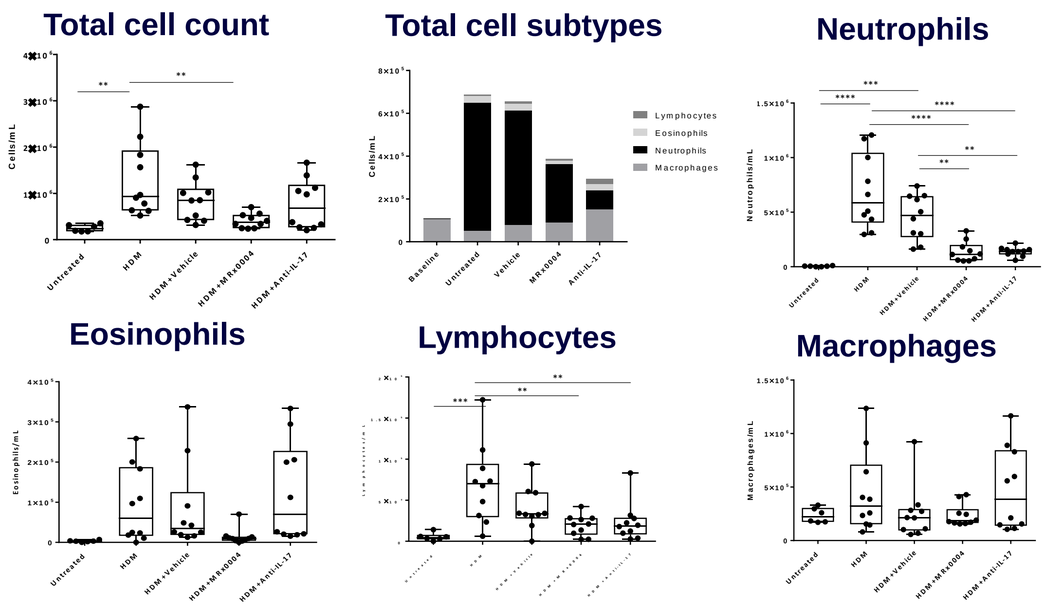
Study design

Daily oral dosing with vehicle or MRx0004



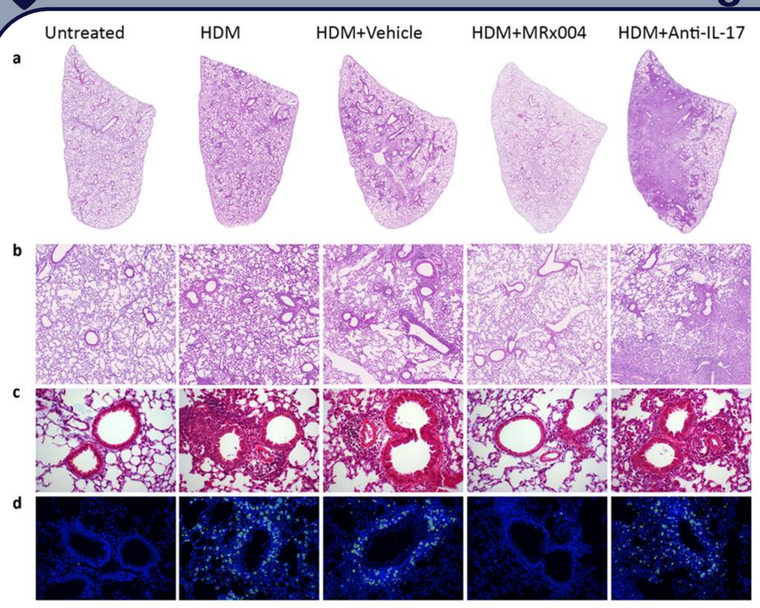
Preclinical model of severe asthma delivers a disease phenotype with elevated neutrophilic and eosinophilic lung infiltration, lung histopathology and a mixed Th1/Th17 cytokine profile. 5 animals/group (3 for baseline), HDM = house dust mite, CFA = complete Freund's adjuvant, stats = ANOVA followed by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

Prophylactic dosing reduces lung infiltrates



- MRx-4DP0004 treatment significantly reduces total cell number in the lung, lung infiltrating neutrophils, and lymphocyte numbers in the lung

Reduction of neutrophil and eosinophil lung infiltrate associated with lung inflammatory scores

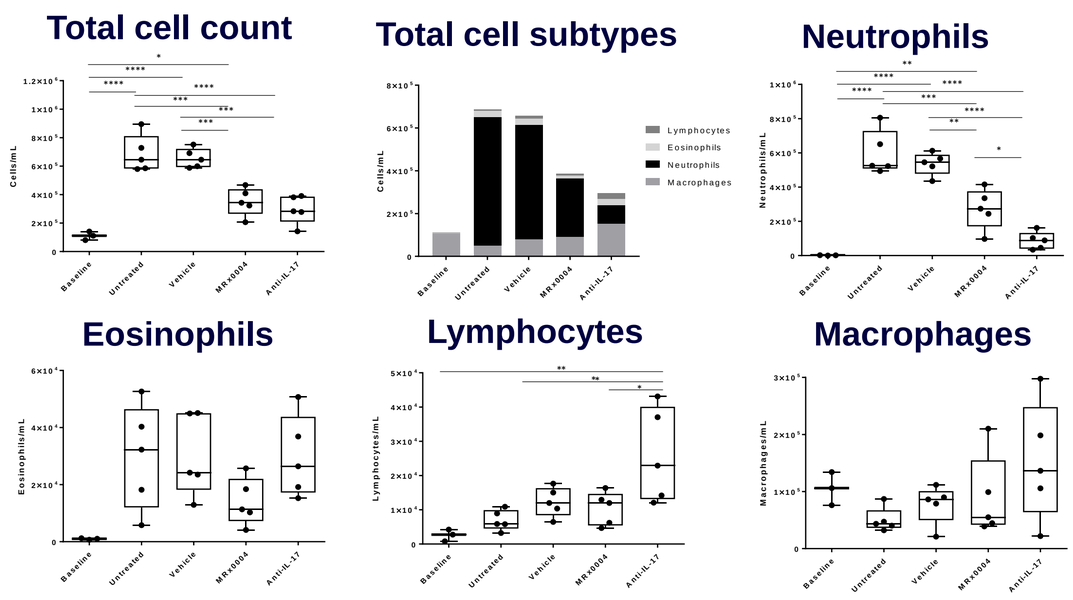


Histopathological analysis of lungs of mice exposed to HDM, and treated with MRx-4DP0004, anti-IL-17 or vehicle, with samples collected 24 h after final exposure. (a) Representative scans (original magnification x25) of H&E stained FFPE sections of left lungs; (b) digital zoom of the lung mid region; (c) representative images (original magnification x200) for histopathology scoring; (d) immuno-labelled CD4+ cells (green), double-labelled with DAPI (blue); (e) mean inflammatory scores. Capped bars illustrate the maximum and minimum data points within each treatment group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ between treatment groups.

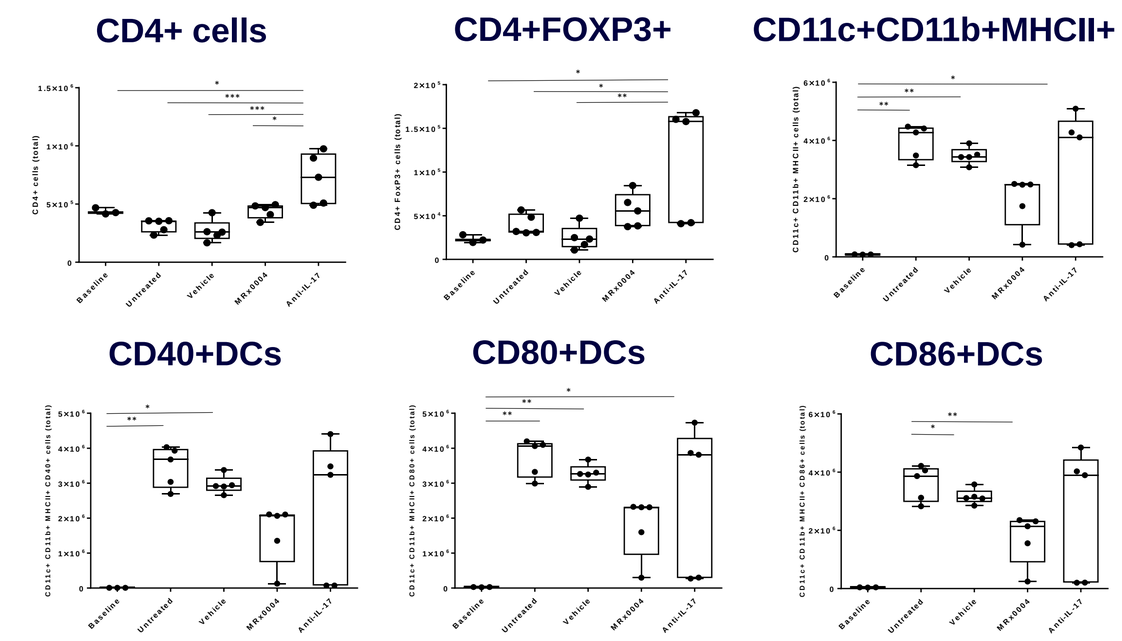
About 4D Pharma PLC

4D Pharma PLC is a pharmaceutical company focused on developing Live biotherapeutic products (LBPs) derived from the human gut microbiome. LBPs 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 four clinical stage programmes (in IBS, IBD, asthma and immuno-oncology) and a strong pipeline of pre-clinical programmes in autoimmunity, inflammation, oncology and CNS disease.

Therapeutic dosing reduces the number and activation state of pulmonary T cells and DCs



- Therapeutic dosing of MRx-4DP0004 significantly reduces total cell numbers and neutrophils infiltrating the lung whilst reducing eosinophilic infiltration.



- Therapeutic dosing of MRx-4DP0004 reduces the number and activation state of pulmonary T cells and DCs

Conclusions

MRx-4DP0004 was tested prophylactically and therapeutically by oral gavage in a house dust mite mouse model of severe asthma.

- We have demonstrated that treatment with MRx-4DP0004, a microbiota-derived bacterial strain, can reduce both neutrophilic and eosinophilic infiltration in lung bronchoalveolar lavage fluid in a severe asthma model.
- Peribronchiolar and perivascular immunopathology was also reduced. MRx-4DP0004 increased lung CD4+CD44+ cells and CD4+FoxP3+ cells and decreased activated CD11b+ dendritic cells. Cytokine analysis of lung tissue revealed reductions of pro-inflammatory cytokines and chemokines involved in neutrophil migration.
- In comparison, anti-IL-17 antibody treatment effectively reduced neutrophilic infiltration and increased CD4+FoxP3+ cells, but it induced lung eosinophilia and did not decrease histopathology scores.
- Further mechanistic studies are underway to clarify the effect of MRx-4DP0004 on host immunity and identify the mediators of it's effect on the gut-lung axis
- MRx-4DP0004 is a promising next-generation drug for management of severe asthma.
- A first-in-man clinical trial is planned in asthma for the second half of 2018.