Abstract S113 Table 1 Health related quality of life and exercise capacity at baseline (end-PR) 6 months and 12 months of long-term exercise

	Baseline n=74	6/12 Attenders n=23	p	12/12 Attenders n=19	p	12/12 DNA n=27	p DNA v baseline
Median(range) class attendance	—	**15 (6–21)**	—	**27 (12–41)**	—	0 (0–10)	—
CAT score Mean (±SD)	22.92 (6.9)	16.48 (1.56)	0.002	17.32 (1.80)	0.02	21.59 (7.71)	0.34
CRQ Dyspnoea	3.31 (1.36)	3.7 (1.73)	0.22	3.33625 (1.18)	0.96	3.37 (1.58)	0.96
CRQ Fatigue	4.01 (1.48)	4.10 (1.37)	0.82	3.78 (1.61)	0.62	3.59 (1.37)	0.21
CRQ Emotional Function	4.66 (1.44)	4.84 (1.42)	0.79	4.52 (1.81)	0.77	4.46 (1.52)	0.51
CRQ Mastery	4.74 (1.64)	5.28 (1.51)	0.79	4.86 (1.47)	0.77	4.75 (1.78)	0.51
HADS Anxiety	7.45 (4.78)	4.9 (3.45)	0.04 ↓	6.17 (4.51)	0.37	10.32 (6.02)	0.04 ↑
HADS Depression	5.61 (3.91)	4.73 (3.11)	0.41	5.88 (3.19)	0.63	6.93 (4.65)	0.24
6 MWT (metres)	352.7 (108.0)	329.6 (78.1)	0.11	321.3 (78.8)	0.14	283.1 (94.1)	0.001

Improvement in pt condition indicated by: ↓ CAT, HADS; ↑ CRQ, 6MWT

Results Contrary to initial hypotheses T_H17 cell frequencies did not differ between health and any asthmatic phenotype, in any tissue compartment. T_H2 cell frequencies were elevated in asthma in bronchoalveolar-lavage (BAL) (ANOVA p=0.041) and markedly in bronchial biopsies (p=0.048), as expected[1]. BAL T_H1 cell frequencies were also increased in asthma (p=0.01) as described[2], whilst T_{REG} frequencies were lower in severe asthma (p=0.019).

T_H2 cytokines were increased in asthma in sputum (IL-5 p=0.005) and BAL (IL-5 p<0.0001, IL-13 p=0.017), but IL-17 was elevated only in BAL in steroid-naive, mild asthmatics (ANOVA p=0.04) who were older (p=0.039).

Longitudinal follow-up revealed no significant differences in T-cell frequencies during exacerbations, though sputum T_H17 cells tended to increase (NS).

We observed that frequencies of Vα7.2+CD161+ (MAIT) cells in blood are lower in asthma than in health (p=0.013), and correlated with severity in blood (p for linear trend <0.0001), and sputum (p=0.018, Figure 1). This deficiency is specific to MAIT cells, and is not related to age or inhaled steroid therapy.

Conclusions A role for T_H17 cells in asthma, particularly severe neutrophilic disease has been widely hypothesised, but is not supported by these data. High BAL IL-17 levels in older, steroid-naive, mild asthmatics may have a different cellular source. We describe a novel finding of deficient Vα7.2+CD161+ (MAIT) cells in severe asthma.

References:

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S115 NADPH OXIDASE 4 OVER-EXPRESSION MEDIATES EPITHELIAL CILIARY DYSFUNCTION IN NEUTROPHILIC ASTHMA

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Objective Epithelial ciliary dysfunction is a feature of asthma and contributes to persistent symptoms and recurrent exacerbations. We sought to examine whether its cause is due to an altered airway environment or an intrinsic abnormality.

Methods Primary epithelial cells were obtained from 46 subjects with asthma and 28 healthy controls for culture. Air-Liquid-Interface (ALI) cultures fully differentiated from human primary airway epithelial cells were stimulated with asthmatic sputum, with or without the presence of antibiotics. Ciliary function was assessed using video-microscopy. Bacterial 16S load in sputum and ALI culture before and after addition of sputum were assessed by qPCR. Oxidative stress was enumerated by 8-oxo-dG expression in bronchial biopsies using immunohistochemiatry in 27 asthmatics and 9 healthy controls, and in basal epithelial cells following hydrogen peroxide (H_2O_2) stimulation assessed by the DCFDA assay. NADPH oxidase (NOX) subtype 4 mRNA expression was quantified using qPCR. The effect of NOX4 inhibition, using GKT137831, on ciliary dysfunction was evaluated using fresh epithelial strips from 13 asthmatics.

Results In *ex vivo* ciliated epithelial ALI cultures ciliary dysfunction did not persist, but was evident in cells from asthmatics following exposure to sputum. Bacterial load increased in the epithelial cultures following exposure to sputum, but were not different between health and disease suggesting that both exposure to an asthmatic environment and a susceptibility to stress is necessary to induce ciliary dysfunction in asthma. *In vivo* the oxidative stress burden in the bronchial epithelium was heightened and related to airflow obstruction and neutrophilic inflammation. NOX4 mRNA expression was significantly elevated in epithelial cells from neutrophilic asthmatics, and H_2O_2-induced intracellular reactive oxygen species generation was increased compared to health and attenuated by NOX4 inhibition. Critically, in fresh epithelial cells from asthmatics inhibiting NOX4 markedly improved ciliary function and was related to the intensity of neutrophilic inflammation.

Conclusions These data suggest that in asthma NOX4 up-regulation promotes the susceptibility of the bronchial epithelium to develop ciliary dysfunction in the presence of an abnormal microenvironment. NOX4 inhibition attenuates ciliary dysfunction. This implicates NOX4 as a potential therapeutic target for asthma, particularly in those with neutrophilic predominant disease.