repeated NTM isolation. Treatment success remains unsatisfactory due to side effects.

This study aimed to explore host factors in patients with NTM isolates and to review treatment completion.

Methods Single region retrospective analysis of patients with NTM isolates from pulmonary source from 2012 to 2017. Comparison was made considering the following factors: age, gender, lung function, autoimmune profile, immunoglobulin levels, immunosuppression, and the presence of cardio-respiratory comorbidities.

Treatment completion was checked through clinic notes. Cases were mapped to explore geographical spread.

Results 90 cases were analysed, 51 females (57%), median age is 72 (IQR 65–78). The commonest co-morbidities were Bronchiectasis (48%), COPD (28%), and Asthma (13%).

The median of forced expiratory volume measured in 1 s (FEV1) was 71% (IQR 48%–87%), 9 patients (10%) had abnormal immunoglobulin levels, 6 (7%) had positive autoimmune screen and only 6 (8%) were immunosuppressed.

At least 13 subspecies were identified. The commonest were Mycobacterium Avium Complex species in 60% cases, then Mycobacterium Chellonae (10%).

4 NTM species were isolated from cases with valvular heart disease. 2 of them had previous aortic valve replacement. One case was of Mycobacterium Chimaera linked to cooler heater units used in aortic valve replacement.

Geographical variation of species and their frequency showed no connection between them.

34 of the NTM cohort (38%) were deemed clinically significant and were started on treatment. Of those, only 9 (26%) completed NTM regime. Further 11 (32%) remained on treatment at time of data analysis while 14 (41%) were intolerant to treatment. At least 19 (56%) of the treated cohort reported side effects.

Conclusion Our data shows that most NTMs were grown from immunocompetent patients with good lung function. Side effects are big barriers to treatment success.

Further work is needed to ascertain treatment success and correlate treatment completion with improvement in lung function and patient-reported measures of quality of life and functional capacity.

Mucosal and microbial drivers of asthma

S27 ADAM33 KNOCKOUT MICE HAVE AN ALTERED METABOLIC TRANSCRIPTIONAL PROFILE IN RESPONSE TO HOUSE DUST MITE WHEN COMPARED TO WILD TYPE MICE

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Rationale *ADAM33* is an asthma susceptibility gene that plays a role in both airway remodelling and susceptibility to allergic airways disease. To study the role of ADAM33 in asthma we have exposed an *Adam33* Knockout (KO) mouse to a house dust mite (HDM) sensitisation and challenge protocol. We have found that these mice exhibit less remodelling, bronchial hyperresponsiveness (BHR) and eosinophilic inflammation than wild type (WT) mice (ER Davies et al., JCI-Insight 2016), however the mechanisms which contribute to this protective phenotype are not well understood.

Methods To study how the response to HDM is altered by loss of *Adam33* we challenged WT and KO mice with HDM or saline and took whole lung RNA samples for next generation RNA sequencing (RNAseq). Gene set enrichment analysis was used to identify pathways and gene ontology terms associated with the differential response to HDM between KO and WT mice.

Results Control WT and KO mice were found to have very similar gene expression profiles at baseline (5 differentially expressed genes, including *Adam33*, FDR $p<0.05$). Differential expression analysis comparing WT saline to HDM treated mice identified the transcriptional profile of the 'normal' response to HDM. The KO response demonstrated a degree of similarity with the WT response (62% of up-regulated genes, 51% of down-regulated gene), including upregulation of hallmark asthma genes *IL13*, *IL5* and *Ccl11*. However, there were also distinct groups of genes modulated only in the WT or the KO in response. Further analysis of the genes identified a predominantly metabolic gene signature, with a particular emphasis on oxidative phosphorylation, where components of the mitochondrial electron transport chain were modulated in opposing directions in the HDM-challenged WT and KO mice.

Discussion The alteration in the pulmonary metabolic gene signature may underpin a shift in immune cell activation and/or modification of smooth muscle energy expenditure during airway contraction. These changes may explain why the KO mouse is protected from both allergic responses and BHR. Further work will aim to identify the source of the different metabolic behaviour at a cellular level and to assess oxidative stress in lungs of normal and Adam33 KO mice.

S28 ADAM33 KNOCK-OUT IS PROTECTIVE AGAINST POST-NATAL AIRWAY HYPERRESPONSIVENESS CAUSED BY MATERNAL ALLERGY

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Background Maternal allergy is a strong risk factor for developing asthma and airway hyperresponsiveness (AHR). *ADAM33* has been identified as an asthma susceptibility gene and is associated with AHR and impaired lung function in early life. Our aim was to investigate the effects of maternal murine allergic airway inflammation on the lungs of offspring before and after birth. We hypothesised that the effects of maternal allergy will be modified in *Adam33* knock out (KO) compared to wild-type (WT) offspring.

Methods Allergic airway inflammation in pregnant heterozygous ($Adam33^{\pm}$) mice was induced by exposure to house dust mite (HDM) through intranasal challenges during pregnancy. Control mice were challenged with saline. WT ($Adam33^{+/+}$)

and KO (*Adam33*$^{-/-}$) offspring from the same litters were studied on embryonic day (ED)17.5 and 2 or 4 weeks *post partum (pp)*. Lung function was measured in response to increasing doses of methacholine and bronchoalveolar lavage fluid (BALF) was collected for differential cell counts. Lung tissue was obtained for RTqPCR, Western blot and immunohistochemistry.

Results At 4 weeks *pp*, WT offspring of HDM challenged mothers showed significantly enhanced AHR compared to WT offspring of control mothers. KO of *Adam33* protected against AHR in the offspring of allergic mothers. *Adam33* mRNA expression was significantly enhanced in WT lungs of HDM challenged mothers at ED17.5, but unchanged *pp*. Differential cell counts in the BALF and mRNA expression of inflammatory mediators indicated an absence of allergic airway inflammation in all of the offspring. Remodelling genes were not affected at any time point studied. In contrast, *Cholinergic Receptor Muscarinic 1 (Chrm1)* mRNA was increased at 4 weeks in all offspring of HDM challenged mothers.

Conclusions This study identifies an *in utero* gene-environment interaction involving *Adam33*. This interaction has implications for the subsequent development of AHR in early life. Further studies are needed to elucidate the precise mechanism(s) whereby ADAM33 mediates its effects. Our data suggest modulation of the contractility of the airways, possibly involving muscarinic receptors.

S29 THE EFFECT OF SOLUBLE ADAM33 ON ALLERGIC AIRWAY INFLAMMATION IN EARLY LIFE IS AGE DEPENDENT

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Introduction Most asthma has its origin in early life and probably involves gene-environment interactions. The asthma susceptibility gene *ADAM33* is associated with bronchial hyperresponsiveness (BHR) and reduced lung function in young children. It encodes a membrane-anchored metalloprotease, which is shed as a soluble protein (sADAM33) whose levels are increased in asthma. We have previously shown that sADAM33, promotes airway remodelling and augments allergic airway inflammation in juvenile mice (Davies ER *et al*, *JCI Insight* 2016). This might be initiated by *ADAM33* induced innate lymphocytes (Kelly JFC *et al*, *Thorax* 2017). The aim of this work was to evaluate the effect of sADAM33 on the allergic airway responses of neonates.

Methods Human sADAM33 was induced in lungs of double transgenic (*Ccsp*/*ADAM33*) (dTg) mice from *in utero* up to 4 weeks *post-partum*. dTg mice or single transgenic (sTg) controls were challenged with house dust mite extract (HDM) 3 times a week for 2 weeks from 3 or 14 days *post-partum*. BHR and inflammation were quantified. Lung tissue was analysed by RT-qPCR and immunohistochemistry (IHC).

Results After HDM challenge from day 3, Type 2-responsive genes *Il-5*, *Ccl11*/*Eotaxin* and *Muc5ac were* significantly increased. Whilst an increase in BHR was observed after HDM challenge, there was no significant difference between sADAM33-expressing and control mice. In contrast, when challenged from day 14, sADAM33-expressing mice had a more robust eosinophilic inflammatory response in the bronchoalveolar lavage fluid with increased *Il-5* and *Ccl11*/*Eotaxin* mRNA expression compared to littermate controls. This was also associated with increased *Acta2* mRNA expression and BHR.

Conclusion These data indicate that s*ADAM33* does not augment allergic responses in neonatal mice as robustly as in older mice. This suggests that the immune microenvironment in neonates is not sufficiently mature to respond to the pro-allergic effects of s*ADAM33* that may induce innate lymphocytes to make the airways more susceptible to allergic airway inflammation.

S30 CEACAM5 (CD66E) MUCOSAL IMMUNOREACTIVITY AND ITS RELATIONSHIP TO ASTHMA

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Introduction The CEACAM immunoglobulin superfamily receptors are involved in cell signalling, cell proliferation and cell repair responses and have relevance to the maintenance of the intact bronchial epithelium. A number of these family members recognise bacteria and, as such, are part of the host defence response. However, some CEACAM-binding bacterial pathogens, in particular *Haemophillus influenzae*, exploit the binding capacity to enhance their chances of colonizing the mucosal surface. As there is increased *Haemophillus* presence within the airways in severe asthma, linked to neutrophilic airway inflammation, we investigated the presence of CEACAM5 within endobronchial biopsies by immunohistochemistry in health and in asthma. CEACAM5 was selected is one of the main bacterial binding immunoglobulins of relevance.

Method Immunohistochemical staining for submucosal CEACAM5 expression was performed on GMA embedded endobronchial biopsies from healthy controls (n=16), mild asthmatics (n=12) and severe asthmatics (n=15). Epithelial immunoexpression (percentage epithelial area using KS400 software) and sub-mucosal positive cell count quantification was undertaken. Sequentially cut sections, stained with neutrophil elastase and CEACAM5, were analysed by the Camera Lucida system to identify the percentage of submucosal positive CEACAM5 cells that were neutrophils.

Results Epithelial immunoreactivity was significantly greater in severe asthma than in health (p=0.027). There was insufficient intact and orientated epithelium to derive quantitative measures in the mild asthmatics. Median CEACAM5 immunoreactive sub-mucosal cell count/mm^2 was significantly higher in severe asthma (37.1 cells), than in both health (15.5, p≤0.001) and mild asthma (23.6, p=0.037). There was no significant difference between health and mild asthma. The median percentage CEACAM5-neutrophil positive submucosal cells in severe asthmatics (n=5) was 52%, with the range being 50%–90.63%.

Conclusion CEACAM5 expression is higher in the epithelium and submucosa of severe asthmatics. This has potential relevance to the altered airway microbiome and biofilm formation in severe asthma. As such, CEACAM5 targeted therapies could be of benefit. Longitudinal studies to understand this relationship would be desirable.