lungs, IL-13 suppressed Adam33 mRNA but no difference in a-smooth muscle actin (aSma) was evident. Immunoblotting for ADAM33 in BALF demonstrated a 76kDa band, consistent with the ADAM33 ectodomain and processed forms at 58/44kDa in dTg animals. ADAM33 enzymatic activity was also significantly increased.

**Conclusion** The data suggest that allergic inflammation induced by IL-13 suppresses Adam33 mRNA expression but induces the release of soluble forms of ADAM33, yielding enzymatically active forms. The release of soluble forms may play a role in airway remodelling, potentially leading to BHR. We next propose to test the effect of specific ADAM33 inhibitors on airway remodelling in this allergic mouse model to assess their potential as novel treatments for asthma.

**Evaluation and treatment of Cystic Fibrosis**

**S119 ROLES OF TLR3, TLR4 AND TLR5–7 IN INTERFERON INDUCTION IN BRONCHIAL EPITHELIAL CELLS AND PERIPHERAL BLOOD MONONUCLEAR CELLS FROM ASTHMATIC AND NON-ASTHMATIC SUBJECTS**

S119

Introduction Defective rhinovirus (RV) induced interferon (IFN)-β and IFN-α production has been reported in primary human bronchial epithelial cells (HBECs) and peripheral blood mononuclear cells (PBMCs) from asthmatics. The mechanisms of defective IFN induction in asthma are unknown. Virus infection can induce IFNs through Toll like Receptors (TLR)3, TLR4 and TLR5–7 and TLR agonists have been identified as potential therapeutic options for asthma. The role of these TLRs in IFN induction in asthma is unclear.

**Objective** To investigate IFN responses to TLR stimulation in HBECs and PBMCs from atopic asthmatic and non-asthmatic individuals.

**Methods** HBECs and PBMCs from atopic asthmatic and non-asthmatic subjects were stimulated with agonists to TLR3, TLR4 & TLR5–7 and type I and III IFN responses assessed by qPCR and ELISA.

**Results** TLR3 and TLR7, but not TLR4, 8 or 9, stimulation induced IFN protein and mRNA expression in HBECs and PBMCs. IFNs induced were IFN-β and predominantly type III IFN-α in HBECs and type I (–α and –β) with no IFN-α in PBMCs. TLR function was not defective in asthmatic compared to non-asthmatic subjects.

**Conclusions** TLR3 & TLR7 were the predominant TLRs involved in IFN induction in HBECs and PBMCs. Defective IFN induction to TLR agonists was not observed in these well controlled asthmatic subjects. TLR3/7 agonists could be effective in inducing IFNs in more severe/less well controlled asthmatics who may have deficient virus induced IFN production.

**S121 LUNG CLEARANCE INDEX TO EVALUATE THE EFFECT OF IVACAFTOR ON LUNG FUNCTION IN SUBJECTS WITH CF WHO HAVE THE G551D-CFTR MUTATION AND MILD LUNG DISEASE**

S121

**Background** Ivacaftor has been shown to lead to significant improvement in lung function, exacerbation rate, weight gain and quality of life in adolescents and adults with CF and the G551D-CFTR mutation.

**Objectives** Drugs targeting the basic defect of CF may hold potential for patients with early stage disease, but establishing benefit is more difficult. If FEV1 is normal, a more sensitive test may be useful. LCI has been shown to become abnormal at an earlier stage of disease than FEV1, and thus may be a more sensitive outcome measure in this group of patients.

**Methods** This Phase 2, randomised, double-blind, placebo-controlled, multicenter, crossover study evaluated the effect of ivacaftor on LCI derived from multibreath washout of SF6 using an Innovoc device. Subjects were ≥6 years with the G551D-CFTR mutation, FEV1 >90% predicted, and LCI >7.4 (upper limit of normal). Ivacaftor 150 mg or placebo was administered twice daily for two 4-week periods with a 4-week washout in between.

**Results** Twenty-one subjects were randomised and 20 received a dose of ivacaftor. Seventeen subjects completed both periods. Mean (SD) age was 16.6 (10.9) years. Mean (SD) baseline LCI was 9.0 (1.5). The treatment effect of ivacaftor for adjusted mean change from baseline in LCI at Day 29 was –2.1 (P<0.0004). Mean

**S120 UPDATE ON THE UK CF GENE THERAPY CONSORTIUM MULTIDOSE, NON-VIRAL, GENE THERAPY TRIAL**

S120

The UK CF GTC has been working for several years to determine the clinical benefit of CFTR gene therapy. Our premise was that for such a therapy to achieve clinical benefit, repeated administration would be required, and that therefore a non-viral approach was needed. We demonstrated in laboratory and preclinical models that GL67A (Genzyme Corp) was the optimal gene transfer agent, and designed a plasmid, pGM169, completely depleted of pro-inflammatory CpG motifs and driven by the novel hCEFI promoter, designed for prolonged expression. In a longitudinal observational study (the Run-in) we measured the variability of multiple outcome measures, both conventional and novel. These data have allowed us to perform power calculations and a) choose our primary outcome (FEV1), b) secondary efficacy outcomes (lung clearance index, various parameters on CT scan, Quality of life questionnaire (CFQ-R), exercise capacity and activity, and selected sputum and serum inflammatory markers), and c) safety measures (clinical findings, exacerbation rate, gas transfer, sputum culture, serum inflammatory markers, renal and hepatic markers). We have recently completed a single-dose safety and dose range study.

In this trial, 150 patients, aged 12 years and above are being randomised in a 1:1 fashion to active treatment or placebo and will receive the nebulised agent at monthly intervals for 12 doses. The group size was determined on the basis of a 6% relative improvement in FEV1. An adaptive design will be used for additional safety; the first 20 patients will receive 3 doses ahead of the rest of the cohort. Patients will be invited to participate in either one or two substudies, being conducted to explore mechanisms; a) nasal administration followed by nasal potential difference (PD) and brushings for mRNA expression and b) pre and post-treatment bronchoscopies for lower airway PD, gene expression and histology. The double-blinded nature of the trial means that final outcome data will only be available upon completion of the study. The trial was initiated in April 2012; here we will update on recruitment, projected time-lines and progress.

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