lungs, IL-13 suppressed *Adam33* mRNA but no difference in *α-smooth muscle actin* (*aSma)* was evident. Immunoblotting for ADAMA33 in BALF demonstrateda 76kDa band, consistent with the ADAM33 ectodomain and processed forms at38/44kDa in dTg animals. ADAM33 enzymatic activity was also significantly increased.

Conclusion The data suggest thatallergic inflammation induced by IL-13 suppresses *Adam33* mRNA expression but induces the release of soluble forms ofADAM33, yielding enzymatically active forms. The release of soluble forms may play a role in airway remodelling, potentiallyleading to BHR. We next propose to test the effect of specific ADAM33inhibitors on airway remodelling in this allergic mouse model to assess theirpotential as novel treatments for asthma.

S119 ROLES OF TLR3, TLR4- AND TLRS7–9 IN INTERFERON INDUCTION IN BRONCHIAL EPITHELIAL CELLS AND PERIPHERAL BLOOD MONONUCLEAR CELLS FROM ASTHMATIC AND NON-ASTHMATIC SUBJECTS

doi:10.1136/thoraxjnl-2012-202678.124

[1]A Sykes, [2]MR Edwards, [1]J Macintyre, [1]A del Rosario, [1]OM Kon, [1]SL Johnston. *[1]Imperial College London and Imperial Healthcare NHS Trust, London, UK; [2]Imperial College London, London, UK*

Introduction Defective rhinovirus (RV) induced interferon (IFN)-β and IFN-λ 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 TLRs7–9 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 & TLRs7–9 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-λ in HBECs and type I (–α and –β) with no IFN-λ 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.

Evaluation and treatment of Cystic Fibrosis

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

doi:10.1136/thoraxjnl-2012-202678.125

[1]EWFW Alton, [1]D Ashby, [2]C Boyd, [3]S Cheng, [4]S Cunningham, JC Davies[1], [5]D Gill, [1]U Griesenbach, [1]T Higgins, [5]S Hyde, [6]JA Innes, [2]G Murray, [2]D Porteous. *[1]Imperial College, London, UK; [2]University of Edinburgh, UK; [3]Genzyme Corp, Framingham, USA; [4]Royal Hospital for Sick Children, Edinburgh, UK; [5]University of Oxford, UK; [6]Western General Hospital, Edinburgh, UK*

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 (FEV_1), 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 ranging study.

In this trial, 130 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 FEV_1. 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.

Funded by the MRC and NIHR through the EME programme.

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

doi:10.1136/thoraxjnl-2012-202678.126

[1]JCD Davies, [2]HS Sheridan, [3]PSL Lee, [3]TS Song, [3]AS Stone, [4]FR Ratjen. *[1]Royal Brompton Hospital and Imperial College, London, UK; [2]University of Edinburgh, Edinburgh, UK; [3]Vertex Pharmaceuticals Incorporated, Cambridge, USA; [4]The Hospital for Sick Children, Toronto, Canada*

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 FEV_1 is normal, a more sensitive test may be useful. LCI has been shown to become abnormal at an earlier stage of disease than FEV_1 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 SF_6 using an Innocor device. Subjects were ≥6 years with the *G551D-CFTR* mutation, FEV_1 >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