S55 TOWARDS THE CLINICAL APPLICATION OF ANTI-PSEUDOMONAL BACTERIOPHAGE: ACTIVITY IS RETAINED FOLLOWING NEBULISATION WITH A RANGE OF COMMERCIALLY AVAILABLE NEBULISER SYSTEMS

[1]R Pabary, [2]A Alegro, [1]EWFW Alton, [3]D Bilton, [2]S Morales, [2]F Smrekar, [1]JC Davies. *[1]Imperial College, London, UK; [2]Ampliphi Biosciences Corporation, Virginia, USA; [3]Royal Brompton Hospital, London, UK*

10.1136/thoraxjnl-2015-207770.61

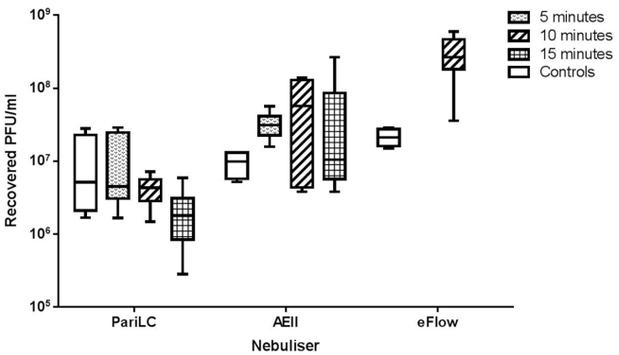
Background and objectives We have recently established safety and efficacy of nasally-inhaled bacteriophage (phage) against *Pseudomonas aeruginosa* in a murine model with reduced infective burden and inflammatory response demonstrated in bronchoalveolar lavage (*Thorax* 2012;67:A50–A51 doi:10.1136/thoraxjnl-2012–202678.108). The aim of this study was to assess titre and activity of four phages following exposure to nebuliser systems more applicable to clinical trial use.

Methods Four phage strains (1–4) were nebulised through a) Pari LC Plus (LCP), b) Aeroeclipse II (AE) and c) eFlow Rapid for up to 15 min. Phages were collected downstream and quantified by standard plaque assay against Pa01. Results were compared with controls exposed to the nebulisation chambers for 15 min.

Results All phages retained efficacy post-nebulisation. Nebuliser type affected recovered titres:

- LCP caused significant decrease in titres of phage 1 and 2 within 5 min and phage 3 within 15 min ($p < 0.05$). Phage 4 titre did not drop.
- AE, despite similar mode of action to LCP, was not as detrimental to titres. Decrease in phage 1 titre was seen within 15 min, phage 2 within 10 min ($p < 0.05$). Phage 3 and 4 did not decrease ($p > 0.05$).
- eFlow does not continuously nebulise and recirculate phage, hence changes in titre over time were not recorded. No titre decreases were observed at end of nebulisation ($p > 0.05$).
- Morphology may play a role in maintenance of phage titre post-nebulisation (1 and 2 *Myoviridae*, 3 and 4 *Podoviridae*).

The Figure 1 shows changes in titres of phage 3 over time following nebulisation through each system.



Abstract S55 Figure 1

Conclusions Phage efficacy was retained after nebulisation though titres dropped, greatest for LCP and least for eFlow (which fell within variability of the methodology (± 0.5 log)). We confirm that phage can survive nebulisation and that this mode of administration may therefore be appropriate for future clinical trials.

S56 MOVING LENTIVIRAL-BASED GENE THERAPY INTO A FIRST-IN-MAN CF TRIAL

[1]U Griesenbach, [1]EWFW Alton, [2]JM Beekman, [3]AC Boyd, [1]M Chan, [1]JC Davies, [4]LA Davies, [3]HE Davidson, [5]JF Dekkers, [1]S Gea-Sorli, [4]DR Gill, [6]M Hasegawa, [1]T Higgins, [3]L Hyndman, [7]G McLachlan, [6]M Inoue, [4]SC Hyde, [1]C Moran, [1]C Meng, [1]MC Paul-Smith, [4]IA Pringle, [1]KM Pytel, [1]A Rodriguez-Martinez, [3]BJ Stevenson, [6]S Tsugumine. *[1]Imperial College, London, UK; [2]Department of Pediatric Pulmonology, University Medical Centre, Utrecht, The Netherlands; [3]Medical Genetics, Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, UK; [4]Gene Medicine Group, NDCLS, John Radcliffe Hospital, University of Oxford, Oxford, UK; [5]Laboratory of Translational Immunology, Wilhelmina Children's Hospital, University Medical Centre, Utrecht, The Netherlands; [6]DNAVEC Corporation, Tsukuba, Japan; [7]Developmental Biology Division, The Roslin Institute Roslin, Edinburgh, UK*

10.1136/thoraxjnl-2015-207770.62

The UK CF Gene Therapy Consortium has developed a pipeline of vectors to deliver CFTR into the airway epithelium. The first of these (plasmid/liposome complexes) recently completed a Phase IIb trial. Anticipating that increased efficiency of gene transfer will be required, we have developed an F/HN-pseudotyped lentivirus which is ~2 logs more efficient in lung gene transfer than non-viral vectors, a single administration lasts for the lifetime of a mouse, and can be repeatedly administered. This vector is targeted for a first-in-man study in 2016, and in preparation for this we have assessed (1) selection of the most efficient promoter/enhancer for lung gene transfer, (2) assessment of toxicity "benchmarked" against the leading non-viral formulation including mapping of integration sites, (3) determination of transduction efficiency which will be used to inform dose-ranging in the trial and characterisation of the cell types transduced by the vector, (4) understanding the impact of pre-existing and acquired anti-viral immunity on transduction efficiency and toxicity, (5) confirmation of CFTR expression and function in relevant models and (6) comparison of vector stability in a jet and single-pass mesh nebuliser. Data will be presented for each of these components, which we believe support progression into human studies. Trial design as well as a regulatory-compliant toxicology study will also be discussed.

Clinical studies in COPD

S57 SHORT-TERM CLINICALLY IMPORTANT DETERIORATION PREDICTS LONG-TERM CLINICAL OUTCOME IN COPD PATIENTS: A POST-HOC ANALYSIS OF THE TORCH TRIAL

[1]I Naya, [2]L Tombs, [3]P Jones. *[1]GlaxoSmithKline, Stockley Park, Uxbridge, UK; [2]Precise Approach Ltd on Assignment at GlaxoSmithKline, Uxbridge, UK; [3]Institute for Infection and Immunity, St George's University of London., London, UK*

10.1136/thoraxjnl-2015-207770.63

Background COPD is a progressive disease leading to adverse outcomes such as exacerbations and death. Numerous predictors of these outcomes have been identified, based on observations at single time points, but little is known about disease trajectory as a predictor of long-term outcome. We hypothesised that the occurrence of a composite measure of clinically important deterioration (CID) made up of moderate/severe exacerbations, worsening of FEV_1 or St George's Respiratory Questionnaire (SGRQ) total score measured over 6 months may predict future long-term adverse outcomes.

Method A *post hoc* analysis of the TORCH data, in all four treatment arms, was performed in 5292 (86.5%) of the 6112