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*

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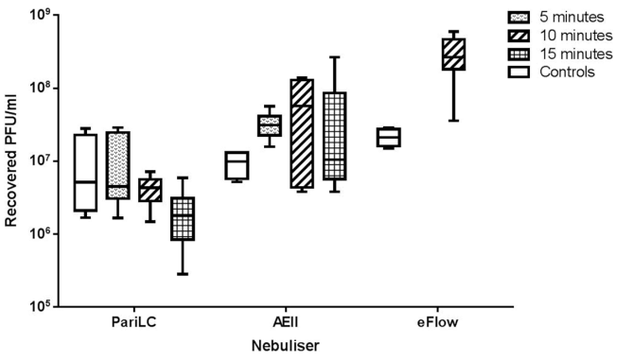
Background and objectives We have recently established safety and efficacy of nasally-inhaled bacteriophage (phage) against *Pseudomonas aeruginosa* in a murine model with reduced infective burden and inflammatory response demonstrated in bronchoalveolar lavage (*Thorax* 2012;67:A50–A51 doi:10.1136/thoraxjnl-2012–202678.108). 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*

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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*

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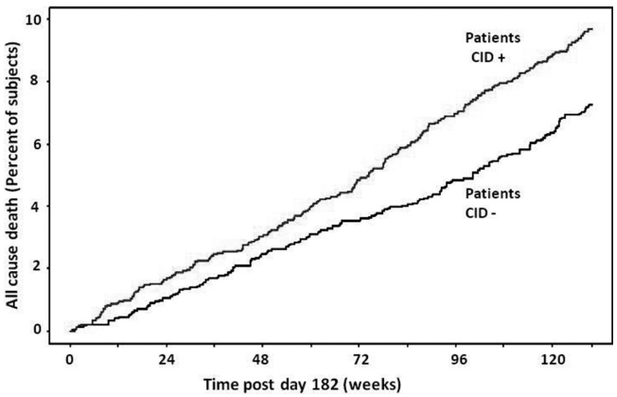
Background COPD is a progressive disease leading to adverse outcomes such as exacerbations and death. Numerous predictors of these outcomes have been identified, based on observations at single time points, but little is known about disease trajectory as a predictor of long-term outcome. We hypothesised 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

COPD patients in the study at 6-months (day 182). CID was defined as: decrease of ≥100 mL in post-bronchodilator FEV_1, or increase of ≥4 units in the SGRQ, or a moderate/severe exacerbation. Using day 182 status, we tested the association between the occurrence of any CID type at or before 6 months and outcomes over the next 30 months including: sustained deterioration in FEV_1 and SGRQ scores, moderate/severe exacerbations and mortality. A Cox's proportional hazards model used day 182 deterioration status with covariates collected at day 182, smoking status and geographical region to estimate future risk.

Results By day 182, 2870 [54%] patients had experienced a CID (CID+) and 2422 [46%] had not (CID-). 30 months later, the CID- group had a LS mean post-bronchodilator FEV_1 117 ml (95% CL 100,134; $p < 0.001$) higher compared to the CID+ group and the SGRQ total score was 6.4 units (95% CL 5.4, 7.5; $p < 0.001$) better. Over the same period, post CID+ patients had a 61% (95% CL 50, 72%; $p < 0.001$) increased risk of a new moderate/severe exacerbation and a 41% (95% CL 15, 72%; $p < 0.001$) increased risk of all-cause death vs. the CID- group (see Figure 1).



Abstract S57 Figure 1

Conclusion Patients experiencing a clinically important deterioration early in the TORCH trial appeared to be set on a clinical path of sustained deterioration in both health status and FEV_1 with an increased medium/long-term future risk of exacerbations and all-cause death.

S58 THE PEARL SCORE PREDICTS 90 DAY READMISSION OR DEATH FOLLOWING HOSPITALISATION FOR AN EXACERBATION OF COPD

[1]C Echevarria, [1]J Steer, [2]K Heslop-Marshall, [2]SC Stenton, [3]PM Hickey, [3]R Hughes, [4]M Wijesinghe, [5]RN Harrison, [6]N Steen, [6]AJ Simpson, [6]GJ Gibson, [1]SC Bourke. *[1]North Tyneside General Hospital, Newcastle, UK; [2]RVI, Newcastle, UK; [4]Royal Cornwall Hospital, Cornwall, UK; [5]University Hospital of North Tees, Stockton-on-Tees, UK; [6]Newcastle University, Newcastle, UK; [3]Northern General Hospital, Sheffield, UK*

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Background Exacerbation of COPD is the second commonest reason for hospital admission, with high subsequent readmission and mortality rates among those who survive to discharge. Risk stratification would inform efficient use of services.

Methods Consecutive patients admitted with an exacerbation of COPD who survived to discharge were recruited by screening admissions units and searching coding records. Six UK hospitals took part: the derivation and internal validation cohort involved the same two hospitals at different time periods, and the external validation involved four hospitals.

Clinical data, and 90-day death and readmission rates were recorded. Multivariate logistic regression analysis was used to develop a tool to predict 90-day readmission, or death without readmission. Performance was assessed by the area under the receiver operator characteristic (AUROC) curve.

Results 2,417 patients were analysed (derivation 824, internal validation 824, external validation 791). Female 54.0%, mean (SD) age 72.6 (10.2) years, FEV1 45.3 (18.2) %predicted, 90-day readmission or death 38.7%.

In the derivation cohort, the five strongest predictors (odds ratio, 95% confidence interval given for whole population) were: two or more Previous admissions in the preceding year (OR 3.17, 95% CI 2.59–3.87), stable-state dyspnoea assessed by the Extended MRCD score (eMRCD 4 OR 1.46, 95% CI 1.12–1.90; eMRCD 5a OR 2.35 95% CI 1.79–3.08; eMRCD 5b OR 3.00 95% CI 2.19–4.11), Age 80 or more (OR 1.48, 95% CI 1.22–1.81), cor-pulmonale "Right heart failure" (OR 1.93, 95% CI 1.41–2.66), Left heart failure (OR 1.45, 95% CI 1.07–1.97). Two or more previous admissions and eMRCD 5b were assigned a score of 3, eMRCD 5a scored 2, while eMRCD 4 and remaining indices scored 1. The risk of readmission and/or death is shown in Table 1.

The AUROC was: derivation 0.73 (95% CI 0.69–0.77); internal validation 0.68 (95% CI 0.64–0.72); and external validation 0.70 (95% CI 0.66–0.73).

Abstract S58 Table 1 90-day death or readmission all patients by PEARL score

Risk	Score		Readmission or death within 90 days	Death within 90 days of discharge	Readmission within 90 days of discharge	Total
Low	0	n	54	7	50	343
		%	15.7	2.0	14.6	
	1	n	130	15	125	547
		%	23.8	2.7	22.9	
Intermediate	2	n	164	46	149	462
		%	35.5	10.0	32.3	
	3	n	155	58	125	352
		%	44.0	16.5	35.5	
	4	n	135	33	120	264
		%	51.1	12.5	45.5	
High risk	5	n	138	24	127	224
		%	61.6	10.7	56.7	
	6	n	90	28	83	131
		%	68.7	21.4	63.4	
	7	n	53	14	49	75
		%	70.7	18.7	65.3	
	8	n	11	6	10	13
		%	84.6	46.2	76.9	
	9	n	6	3	6	6
		%	100	50	100	
	Total		936	234	844	2417
	%		38.7	9.7	34.9	

Discussion In patients hospitalised with an exacerbation of COPD the PEARL score is a robust predictor of readmission and death and may be used to inform efficient use of resources according to risk.