ASSESSMENT OF F/HN-PSEUDOTYPED LENTIVIRUS AS A CLINICALLY RELEVANT VECTOR FOR LUNG GENE THERAPY

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Rationale Our ongoing efforts to improve pulmonary gene transfer thereby enabling gene therapy for the treatment of lung diseases such as cystic fibrosis (CF) has led to the development of a lentiviral vector (SIV) pseudotyped with the Sendai virus envelope proteins F and HN.

Objectives Here, we begin to place this vector onto a translational pathway to the clinic, by addressing some key milestones that have to be achieved.

Main results These include: (1) a single dose produces lung expression for the life-time of the mouse (approximately 2 years), (2) only brief contact time is needed to achieve transduction, (3) repeated daily administration leads to a dose-related increase in gene expression, (4) repeated monthly administration to mouse lower airways is feasible without loss of gene expression, (5) there is no evidence of chronic toxicity during a 2 year study period, (6) F/HN-SIV transduction generates persistent gene expression in human differentiated airway cultures, and human lung slices and transduces freshly obtained primary human airway epithelial cells.

Conclusions The data support F/HN-pseudotyped SIV as a promising vector for pulmonary gene therapy for a number of diseases including CF and we are now undertaking the necessary refinements to progress this vector into clinical trials.

REPEAT ADMINISTRATION OF GL67A/PGM169 IS FEASIBLE, SAFE, AND PRODUCES ENDGENOUS LEVELS OF CFTR EXPRESSION AFTER 12 DOSES

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For gene therapy to improve lung function in CF subjects, repeated administration of the gene transfer agent over the lifetime of a patient will be necessary. This requirement limits the usefulness of adenoviral and adeno-associated viral vectors (both commonly used in CF gene therapy in the past), because these viral vectors induce adaptive immune responses which render repeat dosing ineffective. Thus, for CF gene therapy non-viral vectors are currently the only viable option. We have, therefore, undertaken an extensive pre-clinical research programme to select the most efficient non-viral vector for a Multi-dose CF trial. The cationic lipid formulation GL67A was ultimately chosen and combined with a CpG-free CFTR plasmid (pGM169). We recently completed a single-dose, Phase 2a clinical safety and molecular efficacy study, which demonstrated proof-of-principle for long lasting (several weeks) correction of the CF-specific chloride transport defect, but also indicated that the toxicity-efficacy window is comparatively narrow. To support the trial, we undertook a murine repeat dose (12 doses over 6 months) efficacy, biodistribution and toxicology study. We show that (a) repeated lung administration of pGM169/GL67A is safe and feasible using a clinically relevant nebuliser, (b) achieves reproducible, dose-dependent and persistent gene expression (>140 days after each dose) and importantly (c) allows for a cumulative treatment effect (as measured by levels of vector-specific mRNA) particularly when working in a clinically relevant dosing range (dose 1: 0.8% vector-specific/endogenous mCftr (range 0–1), dose 12: 74% vector-specific/endogenous mCftr (range 31.6–204). The results of this repeat dosing study in the mouse therefore (1) demonstrate that endogenous levels of CFTR mRNA can be achieved by exogenously applied gene therapy (cumulative effect), and (2) affirm the UK CF Gene Therapy Consortium’s strategy of repeat dosing.
Background

There is increasing evidence to support the use of Pulmonary Rehabilitation (PR) in patients with Interstitial Lung Disease (ILD). Several studies have shown significant improvements in six minute walk distance and health related quality of life measures, such as the Chronic Respiratory Disease Questionnaire (CRQ), following PR (Holland et al; 2008). However there is a paucity of data surrounding other outcome measures such as maximal walking exercise tests (the incremental shuttle walk: ISW) or anxiety and depression levels. As the ISW and the Hospital Anxiety and Depression scale (HAD) are commonly used outcome measures in UK PR programmes, the aim of the study was to assess the response of these outcomes to PR in the ILD population.

Methods

We analysed outcome data in 62 (30 male:32 female) consecutive ILD patients completing an 8-week outpatient PR programme. Diagnoses were idiopathic pulmonary fibrosis (n=29), connective tissue related ILD (n=8), sarcoidosis (n=14), hypersensitivity pneumonitis (n=3), asbestosis (n=4), drug induced ILD (n=4). Pre- and post-PR data was analysed using either Paired T-Tests or Wilcoxon Tests.

Results

Only 12 Directors (63%) were aware of trainees with a special interest in CF (26, half currently gaining out-of-programme experience [OOPE]). Northern Ireland (NI) and SE Scotland had most trainees pursuing an interest in CF (22% and 20% respectively), where 75% of these were undertaking OOPE.

Only 1 centre (NI) had changed trainee allocation arrangements to accommodate the 2010 curriculum changes, but despite this trainees rotated to a specialist CF centre in only 12 Deaneries (65%), where the average training time was 3 months. About 180 trainees (50%) did not rotate to a specialist centre, and in these cases Directors reported that individuals were required to make their own arrangements (26%) or had organised day-release or training days (18%).

Conclusions

This survey highlights that, despite the increasing numbers of adult CF patients and the need for suitable training for our future respiratory colleagues now reflected in the curriculum, a significant proportion of trainees in the UK still have limited exposure to CF during their training. Further representations have been made to the training authorities to reinforce the need for increased CF training.

Reference:


Abstract P100 Table 1

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<th>ΔCCQ</th>
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P100 THE CLINICAL COPD QUESTIONNAIRE: RESPONSE TO PULMONARY REHABILITATION

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Background

The Clinical COPD Questionnaire (CCQ) is a 10-item health status instrument which has been shown to be reliable and valid in COPD. It takes only two minutes to complete and is simple to score, ranging from 0 (best) – 6 (worst health status). A change in the total CCQ score of 0.4 or more is considered clinically significant (Kocks et al Respir Res 2006). There is a relative paucity of data assessing the responsiveness of the CCQ to pulmonary rehabilitation (PR). We hypothesised that the CCQ would be responsive to PR and that changes would correlate with changes in other well established health status instruments (Chronic Respiratory Questionnaire: CRQ, St George’s Respiratory Questionnaire: SGRQ and the COPD Assessment Test: CAT).

Methods

75 consecutive COPD patients referred to an 8-week outpatient PR programme were recruited. The CCQ, along with the CRQ, SGRQ, CAT, and incremental shuttle walk (ISW), were measured before and after PR. Paired t-test was used to compare outcomes before and after PR, whilst Spearman’s rank correlation was used to assess association between change in CCQ with change in other health status questionnaires.

Results

53 patients completed PR. Baseline characteristics were 33 Male:20 Female, mean (standard deviation) age 68.5(9.9) years, FEV1% predicted 58 (27) and ISW 224 (178) metres. There was a significant reduction (improvement) in CCQ following PR (Pre: 2.9 (1.3) versus Post: 2.1 (1.2); 95% confidence interval –0.4 to –1.0). Significant improvements were also seen in ISW, CRQ domains, SGRQ and CAT with PR. Changes in CCQ correlated significantly with changes in the other health status instruments (see table 1).

Conclusion

The CCQ is responsive to PR and a practical alternative to longer-established health status instruments.