

P95 ASSESSMENT OF F/HN-PSEUDOTYPED LENTIVIRUS AS A CLINICALLY RELEVANT VECTOR FOR LUNG GENE THERAPY

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Rational 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.

P96 REPEAT ADMINISTRATION OF GL67A/PGM169 IS FEASIBLE, SAFE, AND PRODUCES ENDOGENOUS 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 0–1.8), 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.

P97 TRANSITION FROM A DISTRICT GENERAL HOSPITAL (DGH) CLINIC TO A DISTANT ADULT CENTRE

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Background Transition between CF centres in the same town is well reported but there is less work on transition from large DGH clinics to distant adult centres. Our local paediatric unit provides total care for 60 patients. The majority will move on to the adult centre in a city 45 miles away. Until the last 2 years transition had been taking place very late because low staffing at the adult unit limited outreach support for the local patients who were thus reluctant to move on. The paediatric team felt that although transition was hampered by the lack of a local adult centre an increase in adult staffing was an opportunity to review current practises and identify areas for improvement.

Aims To identify ways in which the transition process could be improved and to explore the need for the introduction of formal transition clinics.

Methods Adolescents (13–18 years) within the paediatric clinic and young adults (18–26 years) who had completed transition to the adult centre in the last two years were surveyed using a pro-forma merging the standards of the CF trust and Department of Health. The CF nurses also completed questionnaires about these patients.

Results 16/19 identified patients took part. CF nurse results showed that only 37% of patients started transition between ages 13 and 16 and only 50% had a key worker. Whilst the nurses felt that they offered most teenagers the opportunity to be seen alone only 14% of patients stated they were seen on their own and most said they would strongly prefer it. Discussions of careers, finance, higher education and fertility took place in up to 43%, but commonly after age 16. Patients reported wanting more information on these topics. Although 60% of patients marked the adult clinic was easy to reach and had appropriate facilities, the 'free comments' section revealed difficulties.

Conclusions There are areas of practise that can be improved in the paediatric clinic independently of the setting up of transition clinics. More teenagers need to be seen on their own and cheque lists are needed to ensure all relevant areas are discussed.

P98 CF TRAINING IN THE UK

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Background As survival in CF improves and the adult population continues to grow, there is an increasing need for the adequate training of chest physicians to care for this patient group. To reflect this, in 2010 the UK respiratory specialist training