TOWARDS A FIRST-IN-HUMAN TRIAL WITH A PSEUDOTYPED LENTIVIRUS

Alton, E.W.1,2; Boyd, A.1,3; Davies, J.C.1,4; Gill, D.R.1,5; Griesenbach, U.1,2; Harman, T.E.1,2; Hyde,S.1,5; McLachlan, G.1,6

1. UK CF Gene Therapy Consortium, London, United Kingdom;
2. Gene Therapy Group, National Heart and Lung Institute,
Imperial College London, London, United Kingdom;
3. Centre for Genomic and Experimental Medicine, IGMM, University of Edinburgh, Edinburgh, United Kingdom
4. CF & Chronic Lung Infection Group, National Heart and Lung Institute, Imperial
College London and Royal Brompton Hospital, London, United Kingdom
5. Nuffield Division of Clinical Laboratory Sciences,
Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom;
6. The Roslin Institute and R(D)SVS, University of Edinburgh, Edinburgh, United Kingdom

The UK CF Gene Therapy Consortium has previously demonstrated that repeated delivery of a CFTR liposome (GL67A) complex can stabilise lung function in a double-blind placebo-controlled Phase 2btrial. However, the magnitude of benefit did not warrant continued progression in the context of the welcome benefit provided by small molecule modulators. We have, in parallel, developed a simian immunodeficiency virus (SIV)-based lentiviral vector pseudotyped with the Sendai-virus envelope glycoproteins (F/HN). In preclinical studies we have shown that:
a) This is considerably more effective at transducing the respiratory epithelium than the clinically benchmarked non-viral GL67A formulation. Specifically, we observe ?15% of target cells transduced in vivo in multiple species
b) This transduction is maintained after three repeated applications
c) Expression is maintained for up to the lifetime of a mouse from a single application
d) We see no evidence for acute toxicity in comparison to GL67A, nor integration site hotspots or clonal expansion. To prepare for a first-in-human clinical trial, we have partnered this product with Boehringer Ingelheim and Oxford BioMedica and are moving rapidly through the preparatory steps including:
a) Developing manufacturing at scale sufficient to support a combined nasal and pulmonary Phase 1/2a study
b) Establishing toxicology protocols suitable for both murine and higher species studies
c) Assessing extra-pulmonary biodistribution and shedding potential
d) Developing single cell transduction assays that can be used in both preclinical studies and the clinical trial
e) Focusing on the initial trial population which will predominantly be recruited from the ~15% of people with CF with unmet need
The above data will be discussed in the context of delivering a gene therapy trial against a background of people with CF, increasingly treated with small molecule modulators