LONG TERM SINGLE DOSE GENE CORRECTION OF THE BIOELECTRICAL CFTR GENE DEFECT IN CYSTIC FIBROSIS MICE

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Introduction

The success of airway gene transfer to correct the bioelectrical defect in cystic fibrosis (CF) mice has not been studied in the same animals over long time periods. We have examined the sustainability of a lentiviral (LV) CF transmembrane conductance regulator (CFTR) gene transfer success via repeated nasal potential difference (PD) measures in individual CF mice over their lifetimes.

Methods

The nasal airway of anaesthetized CF^{tm1unc} mice was instilled with either PBS (control) or 0.3% lysophosphatidylcholine (LPC) 1 hour prior to delivery of a LV-CFTR gene vector. A third group received LPC followed by an empty LV vector control (LV-MT). Nasal PD measurements (Fig. 1a) were assessed at 1 wk & 1, 3, 6, 9, 12, 15, 18 & 21 months after treatment in each mouse. Krebs saline solutions were delivered via the single lumen recording cannula. ΔPD was calculated from the low chloride response under amiloride perfusion.

Results

A continuous partial correction of the chloride channel response (Mean ΔPD of ~ 34% towards normal) was seen in mice receiving LPC and LV-CFTR and persisted for at least 12 months (Fig. 2.,*p<0.05, RM ANOVA). In the two control groups the mean ΔPD after PBS pre-treatment or LV-MT treatment (Fig. 3.) was no different to untreated CF mice (n.s., RM ANOVA). There was no correction of the sodium transport apparent at any time points (Fig 4., n.s. RM ANOVA).

Fig. 1a. Nasal TPD measurement

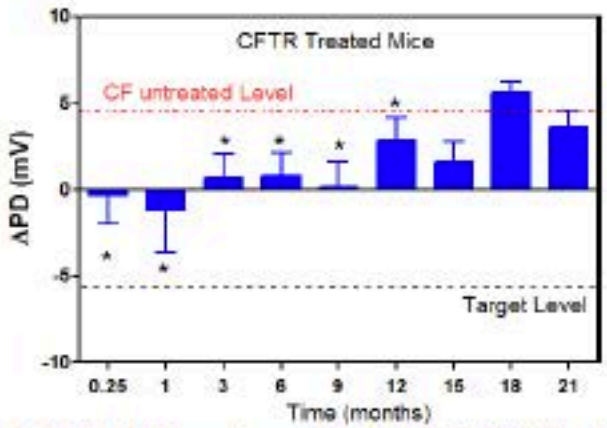

Fig. 2. Partial CFTR correction over time (*p<0.05, RM ANOVA, n=3-12).

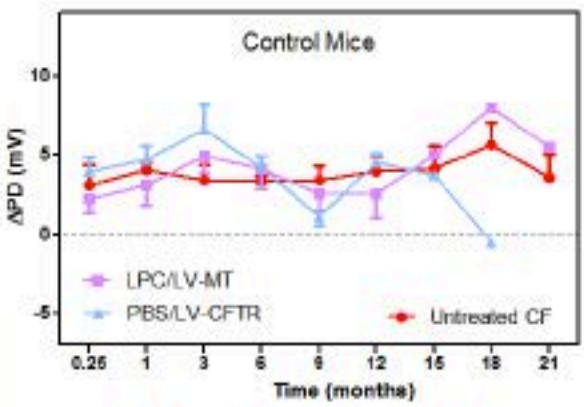

Fig. 3. Control groups over time, n=1-6.

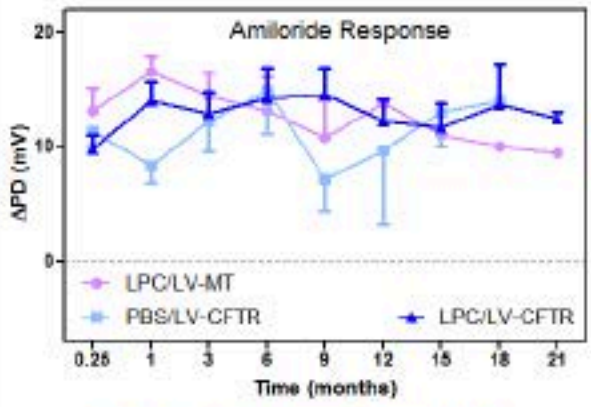

Fig. 4. Sodium Transport Response, n=1-12.

Conclusion

A sustained correction of airway CFTR function persisted for at least 12 months using this LPC/LV-CFTR delivery method. These findings support the feasibility of a long-lasting single-dose gene transfer therapy for cystic fibrosis.

Acknowledgements

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