REPEATED-MEASURE ANALYSIS OF LIFETIME LENTIVIRAL CORRECTION OF THE GENE DEFECT IN CYSTIC FIBROSIS MICE

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Introduction

Examination of successful CFTR gene transfer to correct cystic fibrosis (CF) airway dysfunction disease in CF mice has not been attempted in the same animals over long time periods. We examined the sustainability of gene transfer success via repeated nasal potential difference (PD) measures over their lifetimes.

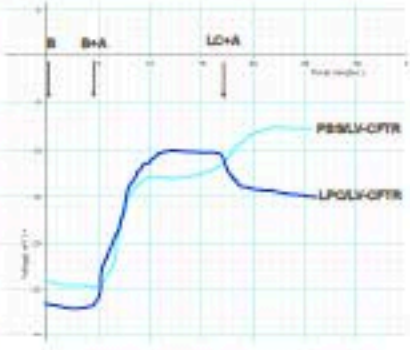
Methods

The nasal airway of anaesthetized CF^{tm1unc} mice was instilled with either PBS or 0.3% lysophosphatidylcholine (LPC) 1 hour prior to delivery of a lentivirus (LV) CF transmembrane conductance regulator (CFTR) gene. In a third group LPC was followed with an empty (MT) LV vector control. Nasal PD measurements (Fig. 1a) were performed at 1 wk & 1, 3, 6, 9, 12 & 15 months after treatment in each mouse. ΔPD was calculated from the low chloride response under amiloride perfusion.

Results

The initial basal PD response was the same in all groups (Fig. 2.), indicating there was no separate LPC effect on PD by the 1 week post treatment point (n.s. ANOVA, (n=6-12/group). In the two control groups, PBS pre-treatment and LV-MT treatment (Fig. 3.), there was no significant change in the ΔPD over time (n.s., RM ANOVA). A continuous partial correction in ΔPD (to ~ 34% towards normal) was seen in mice receiving LPC and LV-CFTR persisting for at least 12 months (Fig. 4.*p<0.05, RM ANOVA).

Fig. 1a. Nasal TPD measurement



1b. TPD Traces from PBS and LPC pre-treated LV-CFTR mice. (B=basal, B+A=basal+amiloride, LC+A=low chloride+amiloride)

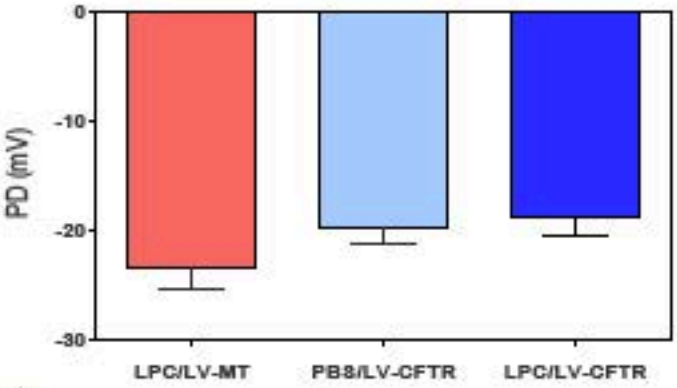


Fig. 2. Basal PD at 1 week, mean +/- SEM, n=6-12.

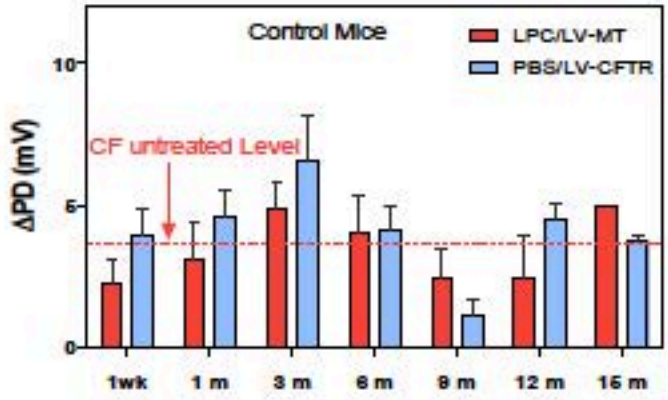


Fig. 3. Control groups over time, n=1-6.

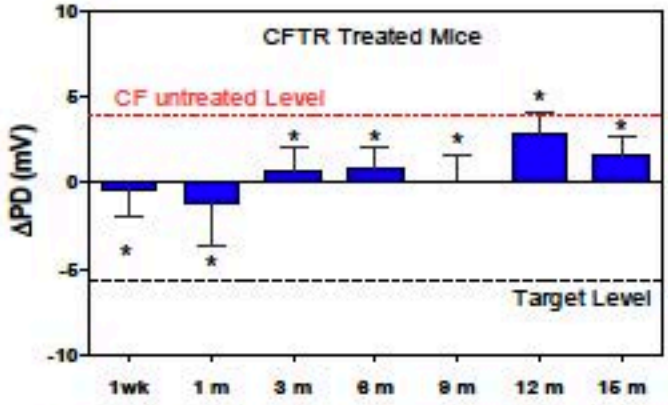


Fig. 4. Partial CFTR correction over time (*p<0.05, RM ANOVA, n=7-12).

Conclusion

In this continuing study we show that sustained partial correction of the CFTR function persists for at least 12 months, supporting the notion of a single-dose gene transfer therapy.

Acknowledgements

NH&MRC and (www.Cure4CF.org)