AIRWAY LENTIVIRAL CFTR GENE TRANSFER EXTENDS THE LIFETIME OF CF MICE

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Introduction

Effective airway gene transfer that could functionally correct the CFTR gene defect in CF airways has been the primary goal of gene therapy development in the CF mouse animal model.

In recent repeated-measure cohort studies we examined the success and effect of extended partial CFTR gene correction in CF mice.

Methods

The nasal airway of anaesthetized CF^{tm1unc} mice was instilled with either PBS (control) or 0.3% lysophosphatidylcholine (LPC - a transduction facilitating pre-treatment) 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 was assessed at 1 wk & 1, 3 and 3 monthly intervals until 21 months following LV delivery. Survival data was expressed as Kaplan-Meier plots. Outcomes were also compared to survival data from Luciferase (Luc) reporter gene studies in 3 groups of normal C57 mice treated similarly but with the Luc gene instead of the CFTR gene.

Results

1) A continuous partial correction of the chloride channel response (Mean ΔPD) was seen in mice receiving LPC and LV-CFTR and persisted for at least 12 months (Fig.1).

2) In the two control groups the mean ΔPD after PBS pre-treatment or LV-MT treatment was no different to that in untreated CF mice (n.s. RM ANOVA).

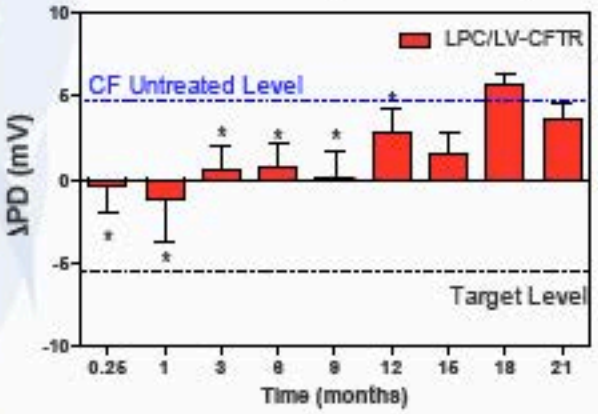

Fig. 1. Partial CFTR correction over time (*p<0.05, RM ANOVA, n=3-12).

3) LPC/CFTR significantly extended median survival (20.1 mo), compared to either PBS/LV-CFTR (14.4 mo) and LPC/LV-MT (8.8 mo) control groups (Fig. 2).

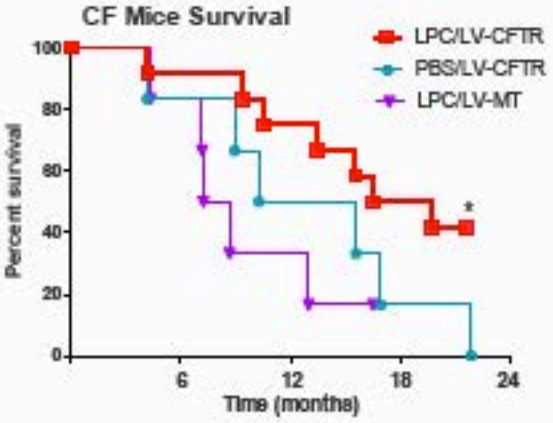

Fig. 2. Survival Curves of CF Mice (*p<0.05 Mantel-Cox log rank, n=6-12)

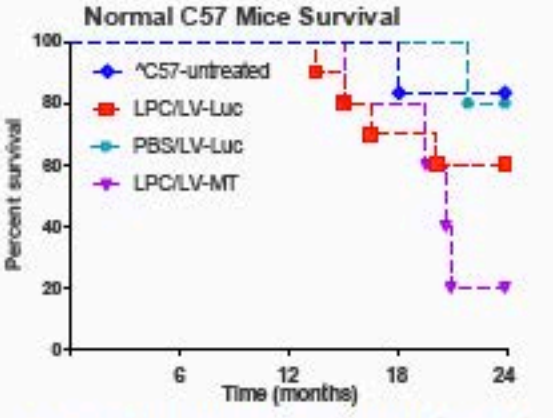

Fig. 3. Survival Curves C57 Mice (^C57 Historical data).

4) Survival in normal C57Bl6 mice similarly treated with the reporter gene Luc was no different between all groups with a median survival greater than 23 months (Fig. 3).

5) The survival of the LPC/LV-CFTR treated CF mice was not significantly different from normal untreated C57 mice.

Conclusion

Successful nasal airway gene transfer in CF mice can significantly improve the lifetime of the treated animals. In this study longevity was boosted to near that of normal C57 mice. This is the first report to our knowledge of a generalised and physiologically significant health improvement in CF animals due to partial correction of airway CFTR dysfunction by any gene transfer. The findings validate the therapeutic utility of LV CFTR gene transfer in a CF disease-specific animal model.

Acknowledgements

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www.Cure4CF.org