IMPROVED SURVIVAL IS BY AIRWAY LENTIVIRAL CFTR GENE TRANSFER IN A CYSTIC FIBR… MOUSE MODEL

Patricia Cmiel…

1. Respiratory and Sleep Medicine, Women's and Children's Hospital, SA
2. Department of Paediatrics, University of Adelaide, SA
3. Centre for Stem Cell Research, University of Adelaide, SA
4. Women's and Children's Health Research Institute, SA

Introductio… …thods

We have shown … long term (> 12 … Male and female CF mice (n=47) were tested under 3 experimental conditions month) par… co… animals were p… …s with the airway surfactant lysophos… be achieved in timed-group studies in (LPC, 0.3%, 4 µl) prior to a lentiviral (20 µl) ve… that contained … CF mice treated with a lentiviral (LV) n=6), or with a saline (PBS, 4 µl) pre-treat… …ior to the ther… vector. CFTR, n=6). The primary treatment group received LPC prior to … In this gene transfer study a Viral titre was 0.6-2.5 x10^{10} TU/ml. CFTR function was assessed by nasal potential repeated-measures study desig… …ce (PD) measurements at 1 week, 3 and 6 months, and then at 6 monthly used to extend our ability to e… …xamis. Mouse group survival was expressed as Kaplan-Meier plots, with survival the effect… to survival data. … Luciferase (Luc) reporter gene studies in 3 groups of … in individual CF mice. C57 mice tre… …similarly but with the Luc gene instead of the CFTR gene.

Results

- Signi… …d persi…ent functional CFTR gene transfer (p<0.05, ANOVA) was present in the nasal airway for up to 12 months (ΔPD … …e 32-54% … towards normal) in CF mice treated with … with LPC/LV-CFTR (Fig.1).
- In the … two control groups the mean DPD after PBS pre-treatment or LV-MT treatment was no different to that in untreated CF mice (n.s. RM ANOVA).
- The functional nasal CFTR gene expression produced by LPC/LV-CFTR was also significanth … …d strongly … in this treated cohort (Fig. 2, p<0.01, r²= -0.92).
- LPC/LV-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 (F…
- Survival in normal C57Bl6 mice … reporter gene Luc was no… median … treated C57 mice (Fig. 4).

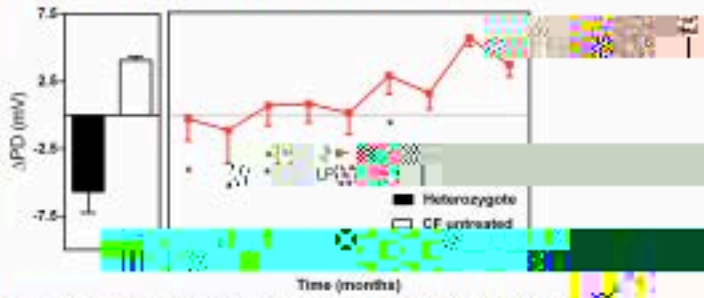


Fig. 1. Partial CFTR correction over time (*p<0.05, RM ANOVA, n=3-12).

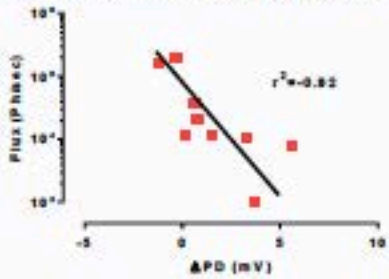
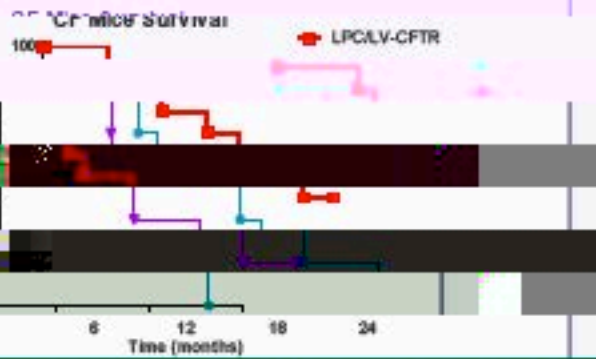


Fig. 2 Correlation of functional correction (ΔPD) response and reporter gene expression (Flux). (p<0.01, Spearman Correlation r²= -0.92).



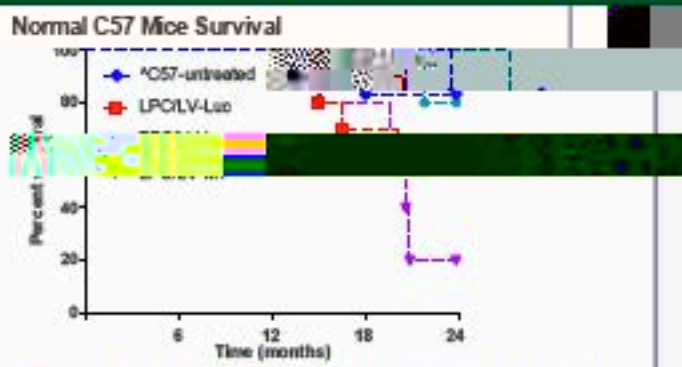


Fig. 4. Survival Curves C57 Mice , n=5-10. (^C57 Historical data).

Conclusion

These results su… …significantly improve lifetimes of treated … …ts. Some nasal dose could reach lung airways and gut … via "spillover" of gene vector to potentially improve CF … function here, with … Further studies are essential to determine the reasons for the substantial improvement in animal survival following such limited airway gene tra…

Acknowledgem…

www.Cure4CF.org

Robinson Institute Travel Grant