DIFFERENCES IN RE-EMERGENCE OF LUNG LUCIFERASE EXPRESSION FOLLOWING NASAL INSTILLATION OF A LENTIVIRAL GENE VECTOR IN NORMAL AND CYSTIC FIBROSIS MICE

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Introduction

Non-invasive bioluminescence imaging has allowed for rapid *in-vivo* quantification of long-lasting gene transfer in experimental animals. We are testing the longevity of a single nasal delivery of our lentiviral (LV) gene transfer system in normal and cystic fibrosis (CF) mouse airways.

Methods

Normal and CF mice received a single nasal pretreatment of control (PBS) or the detergent lysophosphatidylcholine (LPC) one hour prior to delivery of a LV vector containing the reporter-gene luciferase (Luc) at 1.8×10^{10}tu/ml. Imaging to detect luminescence was 10-15 minutes after a 50µl intranasal bolus of the substrate D-luciferin (15mg/ml PBS stock), at 1 week (Fig. 1a, b) and 1, 3, 6, 9, 12 & 15 months post LV.

Results

LPC pre-treatment resulted in significantly greater nasal LV gene transfer compared to PBS pre-treatment at all time points in normal mice and up to 6 months in CF mice (*p<0.05, ANOVA, Fig 2a). Unexpectedly luciferase activity was also detected in the lung in both groups of mice (Fig. 3). At the 6 month time point an increase in lung luminescence was observed in control mice pre-treated with PBS prior to LV in normal mice (*p<0.05, RM ANOVA). Lung luminescence was absent in PBS pre-treated CF mice at the 6 & 9 months, but returned by the 12 month time point.

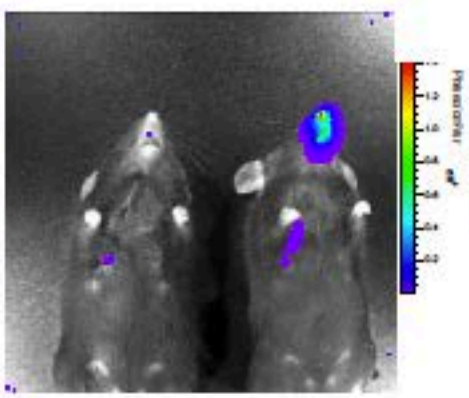

Fig. 1a. LV-luciferase luminescence
Normal mice: PBS (left) vs LPC (right)

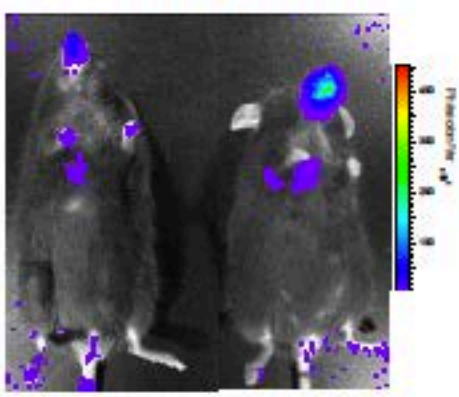

Fig. 1b. LV-luciferase luminescence
CF mice: PBS (left) vs LPC (right)

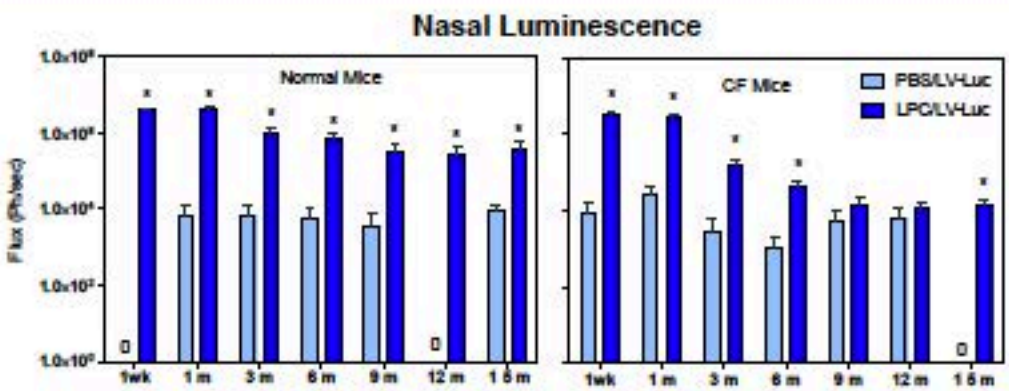

Fig. 2a. Nasal LV-luciferase luminescence. Normal (left) vs CF mice (right), Mean +/- SEM,*p<0.05, ANOVA, n=3-12.

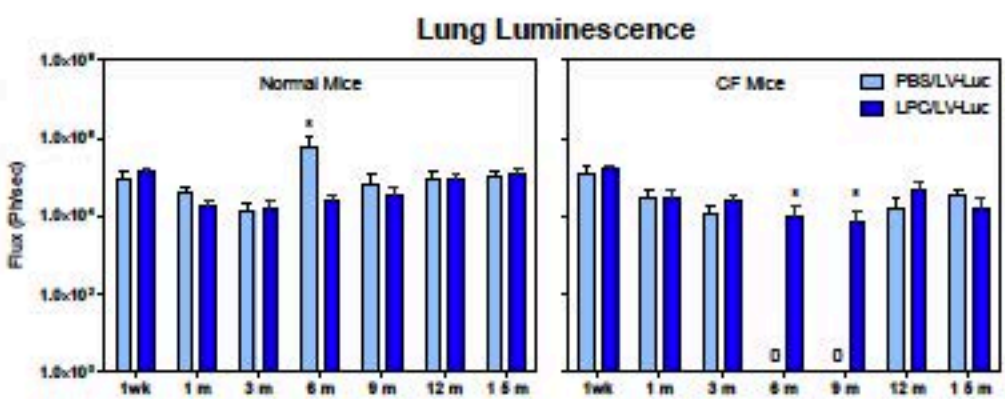

Fig. 2b. Lung LV-luciferase luminescence. Normal (left) vs CF mice (right), Mean +/- SEM, *p<0.05, RM ANOVA, n=3-12.

Conclusions

Long term luciferase gene expression was present in mouse lung with or without LPC pretreatment. Loss, then return of luminescence may indicate an initial (below detection) transduction of lung airway stem cells, with subsequent proliferation of expression within stem cell derived cell lineages.

Acknowledgements

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