Airway Lentiviral CF Gene Transfer In Marmosets

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Introduction

Preclinical studies in non-human primates (NHP) are important in developing clinically-applicable gene transfer protocols for CF airway disease. We report here initial findings from the first studies of LV lung gene transfer performed in the non-human primate the marmoset *Callithrix jacchus* (Figure 1), an animal model increasing in use in gene manipulation studies.

Methods ?? c4CF logo above, CSCR also

LPC pretreatment (0.1%, 200-350 ul) was followed 1 hour later by 350-[illegible] (50ul), each delivered via an ET tube into four anaesthetised animals (2 M, 2F). After 7 days and other organs in two animals were examined for LacZ reporter gene expression via standard X-gal staining. Regular blood samples, secretions and tissue samples were collected for examination of the presence of vector particles.

Results

A rapid but transient O_2 desaturation was present in some animals after LPC administration, however all behavioural and physiological indices were normal post-procedure. Body weights followed usual post-anaesthesia trajectories. Patchy epithelial cell LacZ gene expression was evident en face (Figure 2) and in cross-sections (Figure 3), predominantly [illegible]. No evidence of LacZ gene expression was detected in any other tissues. LV vector-associated protein levels (p24) were present in serum at Day 1 but absent from Day 2 onwards (Figure 4). The Lv gag structural gene was present in trachea and in some tissues of one animal (Figure 6). Further histological, immunological and RT-PCR analyses await completion of the remaining two animals.

Callithrix jaccus

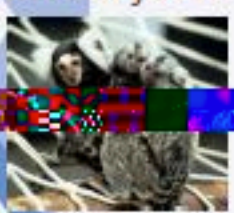

Fig 1: Marmosets. Lifespan ~ 12 years; Body wt's 250 - 350 gm

En face LacZ gene transfer

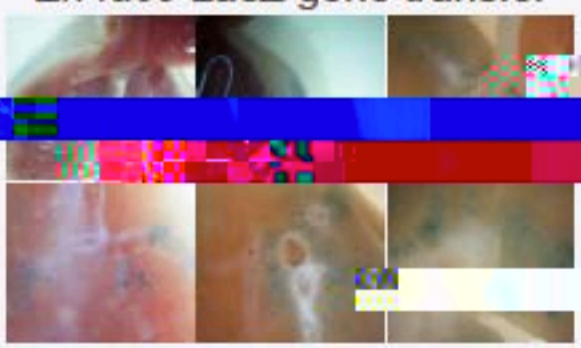

Fig2: En face examples of lung lacZ gene expression.

Xs LacZ gene transfer

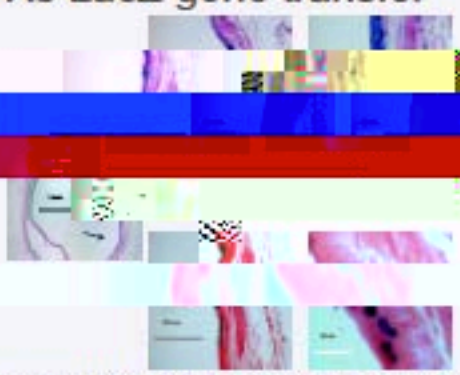

Fig3: Lung lacZ gene expression in cross sections. H/E and Saf-O stained, [illegible] stained and blue cells are transduced.

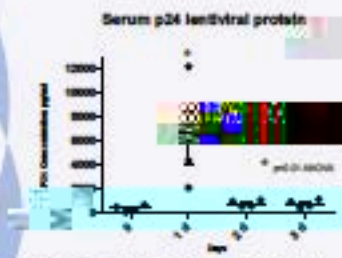

Fig4: Lentivirus P24 protein was briefly present in serum.

Fig5: Vector GAG [illegible] was present in the trachea of [illegible] animals, but in liver and spleen [illegible]

Conclusions

These initial studies suggest LPC/LV dosing procedures are well-tolerated and produces transgene expression in this non-human primate lung. [illegible] animals are being maintained for longer-term assessment of single-dose lung gene transfer. Gene vector components can reach the vascular space after airway dosing, suggesting attention to host immunity and vector safety issues [illegible] warranted. The marmoset appears a suitable animal model for [illegible] clinical

Acknowledgements

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