Repeated Exposure to pDNA/PEI Aerosols Results in Minimal Detectable Toxicity in the Mouse Lung

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INTRODUCTION

The UK CF gene therapy consortium is committed to the testing and development of gene therapy vectors for CF clinical trials

Successful lung gene therapy is likely to require repeated topical delivery of gene transfer agents to the airway epithelium via aerosol delivery

The cationic polymer 25kDa polyethylenimine (PEI) has demonstrated successful gene expression following aerosol delivery to the mouse lung

Clinical development of PEI gene therapies is currently hampered by the perceived toxicity of PEI in vivo

We have investigated lung toxicity associated with repeated, weekly exposure to PEI/pDNA aerosols using a mouse aerosol delivery model

RESULTS

Aerosol delivery to the mouse lung

BALB/c mice (n=6) were exposed to aerosols of pCIKLux/PEI using an 8L perspex whole-body exposure chamber (above)

20 ml of pCIKLux/PEI complexes (0.2mg/ml in water and N:P of 10:1) were aerosolised into the chamber using an Aerotech II nebuliser (CIS-US Inc. Bedford, MA. USA)

Mice were exposed to a single 20ml aerosol every 7 days for up to 10 weeks

CONCLUSIONS

Aerosol delivery of PEI/pDNA complexes results in robust lung gene expression in the absence of detectable toxicity

Chronic exposure to PEI/pDNA aerosols does not result in increased toxicity

Delivery methodology is a critical determinant in PEI/pDNA mediated lung damage

PEI/pDNA aerosols demonstrate potential for a variety of clinical lung gene therapy applications