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**Challenges and progress in developing lung-directed genetic therapies for cystic fibrosis**

Alexandra McCarron1, 2, 3

1. Adelaide Medical School, The University of Adelaide, South Australia, Australia.
2. Robinson Research Institute, The University of Adelaide, South Australia, Australia.
3. Department of Respiratory and Sleep Medicine, Women’s and Children’s Hospital, South Australia, Australia.

Cystic fibrosis (CF) is a genetic disease that affects the lungs and is characterised by frequent infections, airway mucus obstruction and progressive lung function decline. Genetic-based therapies aim to restore the defective CF gene in airway cells, thus preserving lung health. One promising approach under development for airway gene therapy employs use of a lentiviral vector gene delivery system. While significant progress has been made in the field, the lungs pose unique challenges when delivering genetic therapies. Naturally-occuring airway barriers significantly impede uptake and subsequent efficacy of these therapies. A critical area of research focuses on overcoming these barriers to enhance the efficacy of lung-directed genetic therapies.

Three studies were performed to assess or improve the effectiveness of gene therapy in rat airways. (1) Physical perturbation of the airways was performed prior to gene therapy delivery. This was found to provide significant increase in gene uptake by up to 1000-fold. (2) CF lungs are frequently infected with biofilm-producing bacteria and contain mucus that can impede the uptake of some gene delivery vehicles. Rats infected with bacteria were found to have comparable gene expression levels to uninfected rats, suggesting lentiviral vectors are not inhibited by CF lung conditions. (3) Neonatal life stage of gene therapy delivery was investigated to assess the benefits of early intervention in CF rats. Electrophysiological assessments revealed sustained therapeutic correction for up to 12 months.

This work highlights three key areas of research in assessing and improving the efficacy of lung-directed gene therapies for CF. Continued progress will be essential to advance this approach toward first-in-human clinical trials.