

Abstract – Gene therapy for CF: Progress and current challenges

Background: Cystic fibrosis (CF) is a genetic disease caused by a mutation in the transmembrane conductance regulator (CFTR) protein. In airways, this protein is responsible for maintaining lung health by keeping it hydrated. Inadequate functioning of CFTR results in lung surface dehydration leading to chronic infections, inflammation, and premature death most commonly due to respiratory failure.

Gene therapy can be used to insert a correct copy of *CFTR* into the genome to restore organ function by fixing the underlying genetic condition independent of mutation type. Lentiviruses (LV) are used as gene therapy vehicles due to their ability to stably integrate the therapeutic gene into the genome. To offer permanent genetic correction, the basal stem cells of the lung that lie below the epithelial layer, should be targeted as these cells give rise to the future functional cells of the lung.

We have already shown that we can delivery LV containing reporter genes to the lungs of various animals including rats, mice, ferrets, and marmosets. We have been shown that we can also successfully transduce basal cells, but this process remains inefficient. Currently, we transduce a large proportion of alveoli and macrophages *in vivo*. We have a current need to reduce transduction of immune cells, retain the vector within the conducting airways long enough to promote efficient transduction, and hide the vector from the immune system.

Using vector-surface engineering strategies in conjunction with novel delivery methods, we aim to overcome the current challenges of basal cell targeting, immune responses that prevent repeat dosing, and off-target transduction of non-therapeutic cell types. Combatting these critical obstacles will enable full and rapid progress in gene therapy treatment for this life-limiting disease.