

# Cystic Fibrosis Gene Therapy – Not Low-hanging Fruit

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The last 25 years have shown that it has been comparatively slow and difficult to develop cystic fibrosis (CF) gene therapy; the lung is a complex target organ. However, research has steadily progressed and recently it was shown that non-viral gene therapy can stabilise CF lung disease. These data, in addition to the development of potent lentiviral vectors, have renewed interest in CF gene therapy within academia and industry.

## Keywords

Cystic fibrosis, gene therapy, lentivirus, viral gene transfer, non-viral gene transfer, lung gene therapy

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Cystic fibrosis (CF) is caused by mutations in a single gene; treatment burden is high and life expectancy is significantly shortened (median age of survival in the UK is ~40 years). Although CF is a multi-organ disease, chronic lung infection and inflammation are the biggest causes of morbidity and mortality in the developed world. Identification of the disease-causing gene, the cystic fibrosis transmembrane conductance regulator (*CFTR*), over 25 years ago, opened the doors for gene therapy. For decades, CF led the way in this new field. Academia and industry had assumed that the lung would be an easy, non-invasive target, overlooking the fact that potent extra- and intra-cellular barriers interfere with gene transfer into airway epithelial cells.<sup>1</sup> The realisation that CF gene therapy is not 'low-hanging fruit' caused interest to wane and many academics and industry to chase easier disease targets. After the turn of the century, CF gene therapy was pursued by only a small, but highly motivated, number of groups. These teams remained motivated because gene therapy has the potential to tackle the disease at its molecular basis, without requiring a detailed understanding of CF pathophysiology (which is still in flux) or the need to understand how the mutations, of which ~2000 have been identified, affect protein function; gene therapy should be suitable for the treatment of patients with any mutation. In addition, it is likely that low-level gene expression may be sufficient to improve lung disease severity.<sup>2–4</sup>

To date, approximately 27 CF gene therapy trials involving ~600 patients have been conducted.<sup>1</sup> All but two were single-dose phase I/IIa safety studies, which also included assessment of molecular endpoints (measurement of vector-specific mRNA and *CFTR*-mediated ion transport). These trials showed that gene transfer to the CF lung was generally safe and established proof-of-concept for airway gene transfer, but also implied that only low and variable *CFTR* expression (as measured by vector-specific mRNA and changes in ion transport) were achievable. In addition, these trials clarified the strengths and weaknesses of viral and non-viral gene transfer agents for CF gene therapy.

It is now well documented that adenoviral vectors are not suitable for CF gene therapy, due to their immunogenicity, which impacts efficacy on repeated administration.<sup>1</sup> The research community has not yet reached a consensus for adeno-associated vectors (AAV), which is the current vector of choice for a range of eye disorders and haemophilia, for example.<sup>5–6</sup> However, in the context of lung gene transfer, we have not seen any convincing evidence that AAV can be re-administered without loss of efficacy and, therefore, currently question the further development of this vector for CF gene therapy. These data led the UK CF Gene Therapy Consortium (GTC; <http://cfgenetherapy.org.uk/>), which is currently the largest group pursuing translational CF gene therapy, to focus on non-viral gene transfer. The GTC has recently completed the first non-viral multi-dose placebo-controlled phase IIb trial designed to assess whether repeated non-viral gene transfer can alter CF lung disease.<sup>7</sup> The trial reached its primary endpoint (change in lung function as measured by forced expiratory volume (FEV<sub>1</sub>) comparing active and placebo (3.7%, 95% confidence interval [CI] 0.1–7.3; p=0.046) and, therefore, established proof-of-concept that gene therapy can ameliorate CF lung disease. However, the treatment effect was not large enough to warrant immediate progression to phase III studies and further optimisation of dose and dosing intervals will be required. Although adenoviral and AAV vectors are not suitable for CF gene therapy, lentiviral vectors, which integrate into the host cell genome, hold the promise

of persistent expression and efficacy upon repeated administration and are log orders more efficient than the best non-viral formulation.<sup>8-9</sup> Lentiviral vectors have been pseudotyped with various envelope proteins to enable transduction of airway epithelial cells.<sup>8-9</sup> A lentiviral vector pseudotyped with the F and HN proteins from Sendai virus, which has a natural tropism for the airways, is furthest advanced along a translational research path and a first-in-man trial will commence in late 2017.

As discussed, significant progress has been made over the last 25 years, but it is worth discussing a few critical questions, such as:

- How much *CFTR* expression do we need?
- Which cells do we need to target?
- Should studies in CF models form a go-no-go decision point before progression into clinical trials.

In summary, although CF gene therapy is certainly not 'low-hanging fruit', the future looks bright due to proof-of-concept for disease stabilisation after non-viral gene transfer and the development of efficient lentiviral vectors. In addition, interest in CF gene therapy in industry is increasing, which is an essential requirement for rapid progression into pivotal phase IIb trials. □

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