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PERSPECTIVES

With newer tools for gene editing, is it time to revisit genetic therapy for cystic fibrosis?

Cystic Fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7. These abnormalities affect the chloride channels in the mucus producing epithelial cells.[1] With these channels not working properly, water is unable to leave the cells to enter the mucus; thus, leading to sticky mucus which obstructs airways and ducts in the body.[2]

Before considering if gene therapy should be reconsidered for cystic fibrosis, it is important to acknowledge the impact that the disease has on those affected by it. Those suffering with CF experience symptoms early; which in turn leads to absences from school, affecting the child's education and future employment prospects. Around 75% of patients are diagnosed before the age of 2, most commonly by the new-born heel prick test.[3] However, CF is a multi-organ disease. Often patients also suffer from slow growth and failure to gain weight – with bowel symptoms such as diarrhoea, constipation and steatorrhea. When the disease becomes severe; research has shown that there is not only an increase in psychiatric diagnoses e.g. depression, but that they also score poorly on the physical functioning measures of quality of life.[4]

When considering future research in the treatment of CF, it is also important to consider the current treatments that are currently available. With the disease also consisting of a genetic component, finding a definitive treatment has so far proved unsuccessful. Currently, patients rely mainly on preventative measures; ranging from antibiotics, vaccinations, vitamin supplements like A,D,E and K to pancreatic enzymes for aiding their digestion and blood sugar regulation.[2] With the current life expectancy of a CF patient around 37.5 years[5]; compared to the UK national average of 80 years,[6] significant improvement is still required for cystic fibrosis patients' to live normal lives.

As a result, one possible treatment option that is being explored is gene therapy. Gene therapy is still an experimental technique that is being developed to correct faulty genes involved in causing an illness for an individual.[7] In theory, the pathological *CTFR* genes could be replaced by healthy genes in the affected organs, allowing them to function normally. In order for gene therapy to work successfully, three major hurdles have to be overcome; the delivery, getting the gene into the right cells and ensuring the gene is active.[8]

Research has continued to make advances into non-gene therapy treatments for cystic fibrosis patients, with Kalydeco and Orkambi being the first 2 licensed precision medications available in the UK.[9] These medications differ from gene therapy, as their mechanism of action is to help the faulty CFTR protein carry out its function, rather than replace it – as would be the case in genetic therapy. Kalydeco is shown to increase the FEV1% from 55.4% to 64.1%, an increase of 8.7%, which was a significant improvement[10]; a greater degree of improvement than that reported in genetic therapy trails.[11] Despite CF being due to an abnormality of one protein, both of these medications are only available for patients with specific mutations. Gene therapy would allow for all mutations to be targeted potentially acting for a cure for all CF patients, rather than those with just specific mutations. There have currently been more than 25 clinical trials involving over 400 patients attempting to deliver functional CFTR genes.[12]

With advances in medical technology allowing us to code 99.9% of the human genome[13] with more accuracy than ever before, our understanding of genes has never been higher – therefore increasing the chances of successful gene therapy becoming available. As a result, many would argue that it is our ethical and moral duty to continue to attempt developing treatments for currently incurable diseases e.g. cystic fibrosis. If successful genetic therapy can be achieved for cystic fibrosis, a single gene disorder,

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then genetic therapy could be trialled for other single gene disorders e.g. sickle cell anaemia — and could eventually be trialled for more complex gene disorders e.g. cancer.

One such medical advancement of genetic editing is clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (more commonly known as CRISPR-CAS9). Studies have found that whilst CAS9 can accurately cut and paste healthy DNA into cells to treat disease; areas near the DNA repair site were removed, rearranged or inverted[14] — a potential side effect that could lead to dangerous modifications. Thus, another CRISPR enzyme was developed — CAS12a, which has been shown to be more effective and precise in comparison to its CAS9 counterpart.[15] This shows that whilst more research is required to ensure that gene editing can be done safely, advancements are being continuously made which are safer than the previous version.

However, the safety of gene therapy still remains a concern. In 2002, viruses were trialled for the delivery of the genes in X-linked severe combined immunodeficiency disorder patients. The trial resulted in 17 out of 18 patients reporting improvements in their condition, but also resulted in 2 patients developing leukaemia, with one losing their life and the other in remission.[16] In 2015, a new method of gene therapy was trialled — with healthy genes being encapsulated in a layer of fat and delivered via a nebuliser to the lungs. Here, 6 adverse reactions were recorded. Whilst the data monitoring and ethics committee concluded that these were not due to the gene therapy itself, one was possibly due to the bronchoscopy used as part of the trial procedure.[11] To ensure the safe delivery gene therapy in CF patients, more trials are required on living patients. If somatic germ therapy is successful, then germ line gene editing is not required — the technique that raises the majority of ethical objections.

After 12 months of gene therapy using this new technique of gene delivery, there was a 3.7% improvement in the forced expiratory volume in 1 s (FEV1) improvement when compared to a placebo.[11] Whilst this gene therapy did provide some symptomatic improvement, it is small - especially when considering the fact that cystic fibrosis affects numerous other organs in the body e.g. the pancreas and stomach. Thus, different delivery methods for gene therapy needs to be researched to provide full symptomatic relief for affected patients.

Traditionally, gene editing has faced numerous ethical hurdles, similar to those *in vitro* fertilisation (IVF) faced in the initial stages of its development. With IVF, there were huge concerns of "Frankenbabies" being created; with a natural biological process being disrupted.[17] Whilst some still object to the use of IVF, there has been a huge shift in public perception from its introduction; to the point where it is now seen as a positive innovation — helping those who would have otherwise been infertile and helping to reduce the risk of inherited conditions in carriers by removing affected fertilised eggs e.g. cystic fibrosis. Seeing how ethical objections to IVF have shifted, ethical objections to gene editing may shift in the same way.

With the pathophysiology of CF being extensively studied, some argue that genetic therapy would not be required if genetic screening for inheritable diseases was made more readily available. If this was the case, carriers of the disease could opt to have IVF — in order to select healthy embryos from inherited diseases. However, the downside for screening is that many are unaware if they are carriers of autosomal recessive diseases — and therefore mass screening programmes would have to be introduced — potentially at a huge cost, and distress to future parents.

There are many ethical reasons as to why people may be against revisiting genetic therapy for cystic fibrosis. If somatic germ line therapy was developed for CF, it would be a reasonable assumption that the treatment would be expensive, at least initially until further advances in technology made the treatment cheaper. This could lead to the treatment only becoming available for the wealthy; potentially increasing the stigma surrounding the condition for those that cannot afford the treatment. Increasing the stigma around the condition may have negative effects on those that cannot afford the treatment, further increasing the risk of psychiatric issues and decreasing the quality of life for these patients.

In order for successful gene therapy to be available as a treatment for cystic fibrosis, a lot of funding and time is required for it to occur. The latest CF gene therapy trials in 2015 were phase 2b, and the UK Gene Therapy Consortium (GTC) is looking for a pharmaceutical partner to fund the phase 3 of the trial — which can cost an excess of £100 million.[18] CF currently affects around 10,400 people in the UK[19]; meaning it would cost around £10,000 per patient for experimental treatment. It could be argued that money could be spent more efficiently on other conditions that affect more people e.g. sickle cell disease. On the other hand, it could be argued that if successful gene therapy is developed for CF, then the treatment techniques used could help develop gene therapy treatment for other inherited diseases, therefore benefiting more than just the 10,400 people currently affected.

The majority of ethical objections to germ therapy is when germ cells are involved, as the genes then have the potential to be passed onto future generations; and the effect of passing on edited genes is unknown. Whilst gene therapy research is looking at somatic cells, the fear is that the techniques used will be used in gene editing in germ cells — and eventually this will become legal. In 2015, gene editing was made legal for mitochondrial replacement therapy[20] — and the concern is that this will snowball, leading to further legalisation for gene editing. There is also particular worry of "designer babies" being created — which is when genetic interventions occur on pre-implantation embryos to influence the traits of the resulting child[21] e.g. height, intelligence. If the technology was available, it is unrealistic to not expect the wealthiest parents attempting to influence their child's traits; so that they are the healthiest, most intelligent, athletic and attractive they can be.[21] As well as the ethical objections to choosing the traits, it is unknown what the effect of germ line gene editing would be on future generations — especially if there harmful and unforeseen circumstances. Genetic addition was successfully implemented in mice so that they were better at running through mazes, but were made hypersensitive to pain.[21] It is unknown if somatic genetic therapy would lead to similar side effects, possibly changing the personality/reactions to the individual. If

somatic cell gene therapy became more socially acceptable, then social views of germ line gene editing may eventually shift in the same way.

To conclude, there are many scientific and ethical arguments that can be debated for revisiting the treatment potential that gene therapy can offer for cystic fibrosis patients. On one hand, gene therapy has huge potential, with the possibility of improving the quality of life for thousands of patients. If gene therapy was successful in CF patients, it could open the door for more genetic disorders to be treated; beginning with other single gene disorder and moving on to multiple gene disorders. Improvements in gene editing have meant that the process is more accurate and precise than ever before, and that the main areas for future research are the safety of the process and delivery of the genes. Concerns over the safety of genetic therapy remain, with adverse reactions being recorded in recent trails involving genetic therapy. With phase 3 trials expected to cost upwards of £100 million, it has to be debated if that money can be better spent researching other conditions that affect more people, especially in the tough economic climate. Ethical concerns also remain, with the fear of the therapy snowballing to lead to allow designer babies to occur. Overall, in my opinion, if used for the right reasons, the potential for genetic therapy to lead to a cure for cystic fibrosis and numerous other diseases associated with it outweighs the disadvantages.

Conflict of Interests

The authors declare no conflict of interests.

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