Cystic Fibrosis why we're here

Research in focus

Genetic therapies in cystic fibrosis

Fighting for a Life Unlimited

Foreword

Shortly after the cystic fibrosis (CF) gene, called 'CFTR', was identified in 1989, researchers around the world talked about the possibility of a genetic therapy to treat cystic fibrosis. The aim of genetic therapy is to correct the fault in the CFTR gene at a genetic level, meaning the signs and symptoms of the disease are treated or cured. While the field of genetic research has developed enormously in the last 30 years, a genetic therapy for CF is still not available in the clinic.

Gene therapy was the first genetic therapy method to be developed, but a key stumbling block has been how to add new copies of the CFTR gene safely to lung cells. New techniques such as gene editing have since emerged, offering alternative options to treating genetic conditions at the level of genes and DNA.[1]

At the same time as the ongoing development of these genetic therapies, drug treatments to modify the CFTR protein were developed and licensed, such as the drugs Kalydeco and Kaftrio. These drugs are collectively known as 'CFTR modulators'.

We are all incredibly excited about the huge effect that these drugs are likely to have for many people with cystic fibrosis. However, due to the way they work, CFTR modulators aren't suitable for everyone with cystic fibrosis. We have been and will continue to be absolutely committed to funding innovative and world-leading research that will have the same life-changing impact for all people with cystic fibrosis.

With the latest advances in technology for genetic therapies such as the gene editing tool 'CRISPR', today there is real optimism that gene editing and other genetic therapies could be a viable treatment option for people with CF in the next decade. However, the funding challenges brought about by the COVID-19 pandemic have made collaboration and partnerships within research more important than ever.

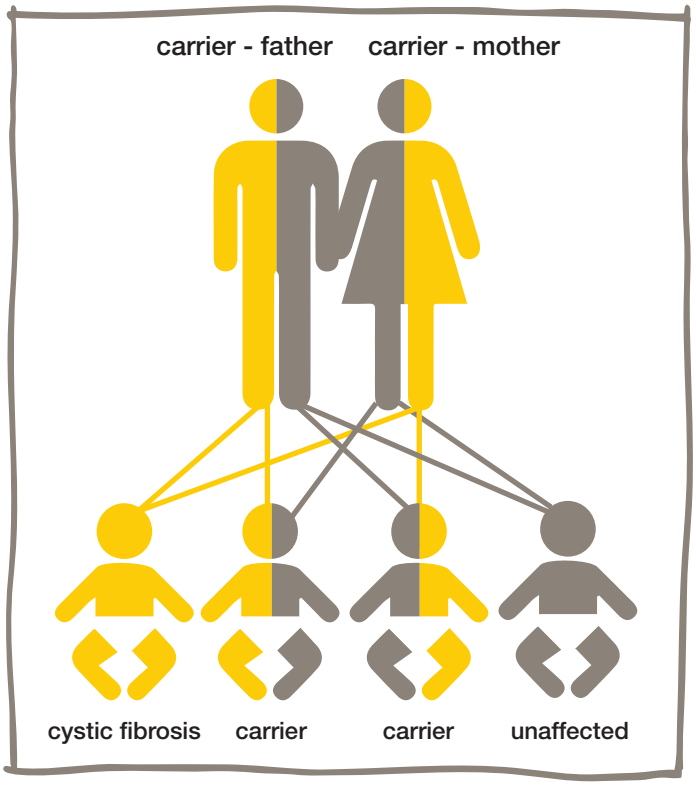
Dr Lucy Allen
Director of Research

What is cystic fibrosis?

Cystic fibrosis is a rare, inherited condition that affects over 10,600 people in the UK.[2] It is caused by a defective gene called 'CFTR', which controls the movement of salt and water in and out of cells. As a result of the defect, the internal organs – especially the lungs and digestive system – become clogged with thick, sticky mucus, resulting in chronic infections, inflammation in the lungs and difficulty digesting food. Some adults with CF may also get cystic fibrosis-related diabetes (CFRD), arthritis, osteoporosis and liver problems.

Genetics of cystic fibrosis

Cystic fibrosis is a 'recessive' inherited disease, which means that it only occurs when a child has two copies of the mutated CFTR gene – one copy from each parent.



Researchers have found mutations in over 2,000 sites along the CFTR gene. Of these, around 360 are known to cause cystic fibrosis.[3] In someone with CF, the CFTR gene from one parent can be damaged or 'mutated' in a different place to the CFTR gene inherited from the other parent. For some people, the place that the CFTR gene is mutated is the same in both of their copies of the CFTR gene.

The types of CFTR gene mutations a person with CF has is known as their 'genotype'. Most people with CF in the UK know their CFTR genotype. Some genotypes are very common, for example around 50% of people with CF in the UK have two copies of the mutation 'F508Del'. Other mutations are extremely rare, where fewer than five people in the UK have the same mutation. The numbers of people with different CFTR mutations vary in different countries, and in people with different ethnicities.[4]

The CFTR gene contains the instruction for making the CFTR protein. In people who don't have CF, working copies of the CFTR protein are made inside the cell and then transported to the surface of the cell. Once they're at the surface of the cell the CFTR protein acts as a channel: a special hole with a 'gate' that allows the controlled movement of chemicals to keep the lungs hydrated. In CF, different things go wrong with production of the protein or how it works, depending on which CFTR mutation (genotype) people have. A mutation in some places within the gene means that no protein is produced. A mutation in other places means that a protein is produced, but it doesn't form the correct shape or can't do its job on the surface of the cells.

Treatments for cystic fibrosis – the need for genetic therapies

The drugs currently available to tackle the underlying cause of CF work in two ways: they either help the faulty CFTR protein get to the surface of the cell, or they help it open the 'gate' when the protein is in position. Drugs like Kaftrio, Symkevi and Orkambi do both. However, these drugs only work if the damaged CFTR gene can make a CFTR protein for them to work on. There are currently no drugs licensed that treat people who have two copies of the CFTR gene with mutations where no protein is produced. These people are part of a group of people described as having rare CFTR mutations, and for whom the development of gene editing treatments is of considerable interest.

"For a medicine such as Kaftrio to have such a positive effect is amazing. Although I'm extremely happy for everybody else, I'm jealous of all the happiness too. None of the new drugs available will have any impact on my CF and my lungs have now deteriorated to a stage where the conversation around transplantation has become necessary. I've had to hide the good news stories from my social media timelines to avoid the heartache.

"My consultant tells me that a lot of work is being undertaken to tackle the remaining mutations. I do hope these treatments benefit the entire next generation of cystic fibrosis sufferers, making options such as transplantation redundant."

Andy, 32, who has cystic fibrosis

In the UK, we estimate that around 90% of people with CF have a genotype that makes them eligible for one of the current drugs. However, some people who have an eligible genotype may not be able to take these drugs. This may be due to the restrictions of the drug licences, where the drugs are not currently licensed for use in children under 12 or to people with CF who have received an organ transplant, for example. Other people who have an eligible genotype may not be able to tolerate the drugs.[5]

Research studies are underway to test the current drugs in samples from people with very rare mutations.[6] While this research may mean that people with more rare genotypes become eligible for the drugs, there will remain a group of people with CF who are not likely to benefit from the current CF treatments. Genetic therapies are an exciting potential treatment for these people.

How might genetic therapies work?

The aim of genetic therapies in CF is to compensate for the faulty CFTR gene and allow a healthy, working copy of the CFTR protein to be produced. If there are healthy copies of the CFTR protein, this means that the lungs would be healthier. There are three broad types of genetic therapy under development, that work in different ways.

Gene therapy involves adding healthy, undamaged copies of the CFTR gene into cells, which allows additional, healthy copies of the CFTR protein to be made.

When the CFTR gene is faulty, the cell's protein-making template called 'mRNA' will also be faulty. **mRNA therapies** work by adding undamaged protein-making templates for the CFTR protein into the cell.

The last broad type of genetic therapy is **gene editing,** also incorporating a newer technique of 'base editing'. The aim of gene editing is to repair the damage to the faulty CFTR gene itself, so it can make a fully-functioning CFTR protein.[1]

For all genetic therapies, a tricky part of their development is working out how to add the necessary components into the cell safely and effectively.

Gene therapy and mRNA therapy approaches will require regular treatments to supply protein-making instructions to cells that are being constantly replaced due to wear and tear at the surface of the lungs. In comparison, gene editing therapies will aim to target lung stem cells. Stem cells are basic cells that can be converted into all the specialist cells that line the lungs, meaning that gene editing therapies offer the potential of a cure for cystic fibrosis.

Gene editing works by making a cut in the DNA at a specific place, making a repair, and then sealing up the DNA cut again afterwards. The technique of gene editing became a much more realistic prospect for treating rare diseases with the development of a biological technique called CRISPR. CRISPR is much easier to 'programme' than earlier gene editing methods and is now the method of choice for developing gene editing therapies.

Progress made in cystic fibrosis gene editing research

To capitalise on the new technique of CRISPR gene editing, the Cystic Fibrosis Trust funded its first gene editing Strategic Research Centre (SRC) in 2016, just four years after the potential of the technique was first established. Strategic Research Centres are virtual centres of excellence bringing together researchers from within and outside of the field of CF with a wide range of skills and expertise. They support scientists and other specialists around the world to work together to address specific issues arising from cystic fibrosis.

This gene editing methods SRC is now finishing. The researchers have shown that it is possible to successfully deliver gene editing tools into lung cells in the laboratory and that CRISPR gene editing methods can successfully repair different types of CFTR gene mutations. They've also shown that repair of these mutations led to the presence of fully-functioning CFTR protein in lung cells. They were able to see this through increased transport of water out of the cell and improved hydration of lung cells grown in a dish in the laboratory.

Focusing in on gene editing therapies

Building on the evidence from the first SRC that a gene editing approach has potential as a treatment for CF, focus has now turned to the practicalities of how to make this a reality.

We have recently announced that we will be co-funding a second SRC to be led by Professor Stephen Hart, building on the success of the previous grant. This second gene editing SRC will be co-funded with the US Cystic Fibrosis Foundation.[7]

"Advancing gene editing therapies is a top priority for the CF Foundation, and it will likely require international collaboration to address fundamental challenges in this area. By working together with the UK Cystic Fibrosis Trust to support this Strategic Research Centre, we are moving one step closer towards our ultimate goal of developing a cure for CF."

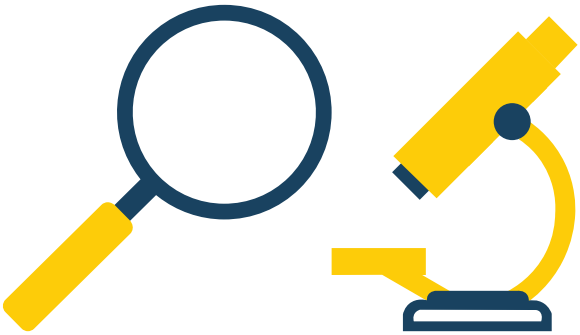
William Skach, MD, Executive Vice President and Chief Scientific Officer of the Cystic Fibrosis Foundation

Professor Stephen Hart

"We have developed a range of tools and gained a lot of experience in applying gene editing in CF; now we need to refine these and work out the best way to proceed towards therapies for cystic fibrosis."

Professor Stephen Hart, Professor of Molecular Genetics at UCL Great Ormond Street Institute of Child Health, London

The team aims to understand how the gene editing methods that they have used successfully in cells growing in a dish might need to be adapted to work in the complex environment of the lungs of someone with cystic fibrosis. In the eight years since the CRISPR gene editing method was first described, the technique has advanced significantly. This means new, more efficient and safer ways of editing the CFTR gene have become available. The researchers will be investigating the best CRISPR methods to correct the widest range of CFTR mutations.



The importance of partnerships

For a successful gene editing therapy to be developed, it is crucial that experts work in partnership together to tackle this really tricky scientific challenge. Alongside advancing knowledge in gene editing methods, cell biologists are developing a more in-depth understanding of how the cells that line the lungs work together, and the best cells to target for gene editing therapies.

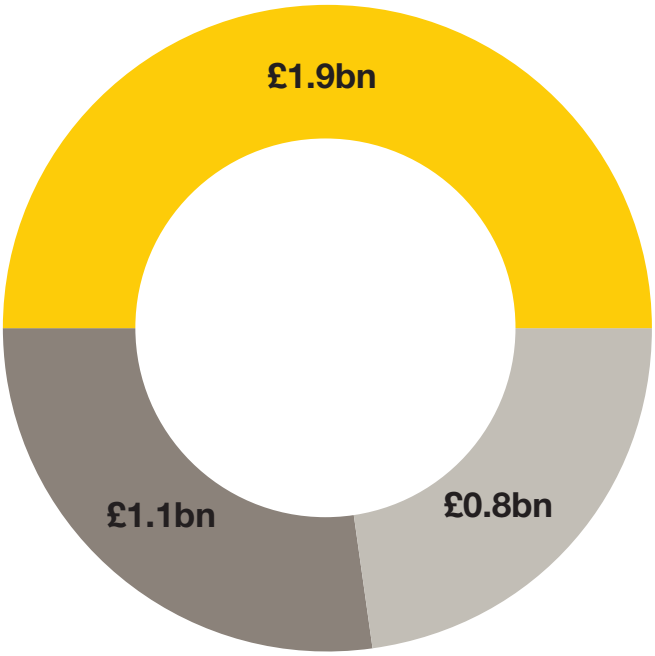
Our SRC funding model brings together researchers with diverse expertise to solve a specific problem or issue in cystic fibrosis. Our analysis has shown that awards of SRC funding have attracted further funding and prestige, and have led to the development of new partnerships for the scientists involved.[8]

Dr Lucy Allen

"Making gene editing a reality for people with CF will take the coming together of expertise from across the world. That's why we're excited about being able to work in partnership with the CF Foundation to fund our newest, collaborative SRC."

Dr Lucy Allen, Director of Research, Cystic Fibrosis Trust

Collectively, research funding from medical research charities, including the Cystic Fibrosis Trust, accounts for 50% of all publicly-funded research in the UK.[9]



AMRC charities account for half of the publicly funded medical research nationally in 2019

£1.9bn AMRC charities

£1.1bn National Institute for Health Research (NIHR)

£0.8bn Medical Research Council (MRC)

For the Cystic Fibrosis Trust, and many other charities, co-funding research provides a way to add more value to the money we invest in research across the world. This co-funding model has never been more needed due to significant challenges faced in charity fundraising from the COVID-19 pandemic and no Government support packages being available.[10]

The dream for gene editing

Last month Professors Emmanuelle Charpentier and Jennifer Doudna, who developed the CRISPR method of gene editing, won the 2020 Nobel Prize in Chemistry, one of the biggest awards in science.[11] In describing the significance of the technology, the Prize Panel shared the hope that it "may make the dream of curing inherited diseases come true". An effective gene editing therapy would allow everyone with cystic fibrosis to live fuller, healthier and longer lives.

References

1. An explainer on genetic therapies and cystic fibrosis https://www.cysticfibrosis.org.uk/news/an-explainer-on-genetic-therapies-and-cystic-fibrosis

2. UK Cystic Fibrosis Registry Annual Data Report 2019, published August 2020. www.cysticfibrosis.org.uk/registry

3. CFTR2 Database: Clinical and Functional Translation of CFTR www.cftr2.org

4. De Boeck K, Acta Paediatr. 2020, 109, 893–899. doi: 10.1111/apa.15155

5. Lopes-Pacheco M, Front. Pharmacol. 2020, 10, 1662. doi: 10.3389/fphar.2019.01662

6. HIT-CF Europe https://www.hitcf.org/ and Cystic Fibrosis Foundation programmes on theratyping, reviewed by Clancy et al J Cyst Fibros. 2019, 18(1), 22-34

7. Cystic Fibrosis Trust announcement of strategic research centre funding for therapeutic gene editing in partnership with the Cystic Fibrosis Foundation https://www.cysticfibrosis.org.uk/news/funding-for-a-focused-approach-for-gene-editing-research-announced-today

8. Cystic Fibrosis Trust analysis of 2013-2018 Research Strategy achievements https://www.cysticfibrosis.org.uk/the-work-we-do/research/where-your-money-goes/how-our-research-has-made-a-difference/research-achievements

9. Association of Medical Research Charities report 'Our sector's footprint 2019' https://www.amrc.org.uk/our-sectors-footprint-in-2019

10. Association of Medical Research Charities blog on their response to the COVID-19 pandemic https://www.amrc.org.uk/blog/medical-research-charities-and-covid-19-amrcs-response-and-key-guidance

11. Nobel Prize in Chemistry 2020 press release https://www.nobelprize.org/prizes/chemistry/2020/press-release/

Contact information:

For more information visit **cysticfibrosis.org.uk/research**
or contact **research@cysticfibrosis.org.uk**.