

Cystic fibrosis (CF) is the most common lethal genetic disorder in Caucasian populations and currently affects around 9,500 young people in the UK. Almost two million people in this country – about 1 in 20 – carry the faulty gene that causes the condition (usually unknowingly) and when two of them have a child, there is a 1 in 4 chance of their baby having CF.

Cystic fibrosis affects the internal organs, especially the lungs and digestive system, by clogging them with thick sticky mucus which readily harbours chronic infections. This makes it hard to breathe and difficult to digest food. Daily treatment, even when 'well', usually entails hours of physiotherapy and a cocktail of drugs including dozens of tablets containing enzymes taken before each meal. Today, those affected generally live to their mid-thirties; there is, however, no cure.

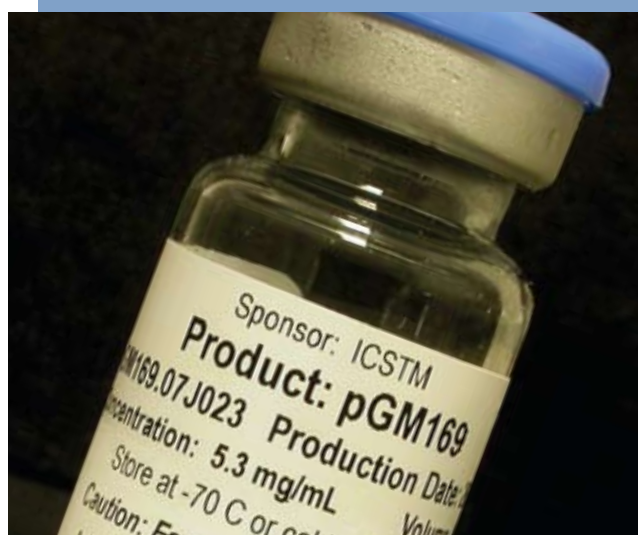
The identification in the late 1980s of the gene responsible for CF opened a window of hope. 'Gene therapy – the use of genetic material such as DNA to treat people – is ideally suited to CF,' says Dr Deborah Gill, who with Dr Stephen Hyde runs the Gene Medicine Group in the Nuffield Department of Clinical Laboratory Sciences. 'We know that the affected individual has two mutant copies of the gene and that inserting a healthy working copy into the cells to make the CF protein would correct the defect.'

The Oxford researchers are expert at investigating precisely what genetic material to insert and how to do it. 'It would be fantastic if we could repair the damaged gene, but what we are actually aiming to do is put a working copy of the gene into a circle of DNA, called a plasmid, and get that inside the appropriate cells,' says Dr Gill. 'A circle of DNA is quite fragile, so we encapsulate it in a liposome – a fat molecule – to protect the DNA. We then create an aerosol, or mist of droplets, which can be breathed into the lung.' When a liposome brushes against a lung cell, it will dissolve on its membrane, slipping past patients' immune systems and sneaking its DNA cargo into the cell.

This current technique is the result of many years of endeavour. An initial flurry of activity worldwide to develop a successful gene therapy stalled as biotech companies and research groups realised that the road to success would be long and hard. Oxford's Gene Medicine Group persisted. In 1993, they demonstrated for the first time that delivery of DNA/liposomes could correct the gene defect in CF transgenic mice. Subsequent studies to introduce DNA/liposomes into the noses of CF patients (where cells are similar to those in the lungs) were also successful, but the effect lasted only days, meaning any treatment would have to be administered repeatedly.

In 2001, the Cystic Fibrosis Trust approached the three UK university groups still working in the area – at Oxford, Edinburgh and Imperial College – and offered to fund their research to the tune of £35m if the groups would collaborate as the UK Cystic Fibrosis Gene Therapy Consortium. That consortium now comprises around 70 clinicians and scientists, of whom 15 are based at Oxford specialising in the design of the plasmid and its delivery technology.

Research is now at an exciting stage. In 2009, the consortium began safety trials of its first product, with CF patients being given a single inhalation of DNA/liposome droplets into the lung to see if there are any harmful side-effects; scientific tests are also checking how long beneficial effects last. 'Our latest plasmid includes an extra sequence so that it's expressed for many months,' says Dr Gill. This trial will be followed by a long-term study of a hundred individuals, each given 12 monthly doses and monitored for clinical benefits. For the first time in the UK, researchers will carry out gene therapy trials with children as young as 12 to try to protect against the lung deterioration experienced by CF patients. 'We really want to crack this,' says Dr Gill. 'We hope that by the end of our trials, in 2012, we will have promising enough results to interest the pharmaceutical companies in working with us to get the treatment to patients.'



## Gene therapy: a window of hope

Techniques being pioneered by Oxford's Gene Medicine Group are tackling the challenge of cystic fibrosis, as *Sally Croft* discovers

**'Families affected by CF have great hopes of this research. Their trust in the researchers involved gives it the best chance of becoming a viable clinical treatment in the not too distant future'**

*Rosie Barnes*  
Chief Executive, Cystic Fibrosis Trust