Interview

Gene therapy for cystic fibrosis: future hopes and milestones

Eric Alton speaks to Sam Rose, Assistant Commissioning Editor

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Department of Gene Therapy, National Heart & Lung Institute, Manresa Road, London, SW3 6LR, UK
e.alton@imperial.ac.uk

Eric Alton is the coordinator of the UK Cystic Fibrosis Gene Therapy Consortium, which brings together the three centers in the UK (Edinburgh and Oxford Universities and Imperial College) focused on this field. Alton is Professor of Gene Therapy and Respiratory Medicine at the National Heart and Lung Institute, Imperial College (London, UK), and Honorary Consultant Physician and Director of the Respiratory Biomedical Research Unit at the Royal Brompton Hospital (London, UK). For over 15 years Alton has moved from inventing a diagnostic test for cystic fibrosis (CF), to developing gene therapy for CF, including two clinical trials. To date, Alton has published more than 130 articles on CF. At the 2011 Medical Futures Innovation Awards; Alton was presented with the Best Translational Research Innovation Award, and the Best Therapeutic Innovation Award (Respiratory). At present, Alton is working towards the first ever clinical trial that will measure therapeutic benefit from long-term gene therapy in CF patients.

■ During your medical training, what initially attracted you to treating cystic fibrosis?

First I started as a general medical doctor, then I specialized in respiratory medicine. I had the privilege of working with someone called Duncan Geddes, who worked at the Royal Brompton hospital, and he first introduced me to the basic defect in cystic fibrosis (CF). He asked if I could put together a diagnostic test to assess this during a 3-month period when he had some funding for me. That was a very long time ago now, and that's what took me into the world of CF.

■ Which came first, an interest in the disease, or an interest in gene therapy itself?

I was looking at the basic defect in CF, which is essentially an electrical one. The protein the CF gene makes, CFTR, conducts chloride ions from inside the cell out onto the cell surface and water follows the chloride by osmosis. So what normal lungs are doing is moving chloride onto our airway surface and hydrating the airway surface, and that means the cilia (hairs) on the surface are normally immersed in water. In CF patients, owing to the genetic defect where they do not make normal CFTR protein, chloride ions do not move from inside the cell to the surface, so water does not move either. Consequently, the cilia are sitting in a suboptimal volume of water and cannot beat normally. That means when CF patients inhale bacteria, these stay within the lungs and cause repeated chest infections, and sadly that is what eventually kills the patient. When chloride moves, because it is negatively charged, you can measure electricity because you are moving an ion across the cell. So I put together a diagnostic test involving measuring the battery power, the electricity, in the airways, which is different in a CF person to a non-CF person. I spent several years working on the basic mechanisms, then the CF gene was cloned in 1989, and that opened the door for CF gene therapy; once you have the gene there is that possibility. The obvious thing was that if we could do gene therapy then we could use this test to find out whether there was more electricity after the gene therapy than before, so they came together. At this point I moved from measuring electricity to doing gene therapy and using the test. That was around the beginning of the 1990s and I have been doing this for almost 20 years.

■ Since the first administration of CFTR gene therapy in 1993, how has this field evolved?

The field has evolved in that we now understand that the key issue is a delivery question. Gene therapy will work; once you put a new copy of the gene into

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the nucleus of a cell there is no question whether it will work. The problem is delivering the new gene into the nucleus because the cells in the airways are made to stop pollutants and bacteria getting in, so why should the cell take up that gene? The evolution of the field has been to understand that it is all about 'delivery, delivery, delivery', and thus to make better delivery vehicles.

The field started with using viruses, and what we have tried to recognize in the UK is that you cannot really use a virus clinically because when you deliver the gene, you only get the protein expressed for 2 or 3 weeks. If you are serious about clinical benefit you have to do it repeatedly, and you cannot repeatedly give a virus because the immune response will increasingly recognize the virus and therefore eliminate it. So one of the things we decided early on was to use nonviral approaches in which the gene is wrapped in fat to deliver it into the lungs. The field has evolved to understand what is the best fat, what is the best nebulizing system, what is the best biomarker to know that the patient is getting better, etc.

Another thing that is really important is that we have evolved a way of working. The UK Cystic Fibrosis Gene Therapy Consortium has brought together different institutions and pretty much everyone in Britain that works on CF gene therapy. It has been a completely new model of working, in that we are not working in competition with each other. We are collaborating and sharing resources; we are not duplicating. I think that has been an exciting evolution.

■ When & why was the UK Cystic Fibrosis Gene Therapy Consortium founded?

It was founded in 2001 and it was because the CF Trust, who have until recently been providing the bulk of our funding, were funding three UK groups at Imperial College London, the University of Oxford and the University of Edinburgh, who were in competition. Rosie Batnes, the former chief executive of the CF Trust, had the very good idea of bringing us all together one evening and suggesting that it would be much more efficient if we worked without duplication and competition, and really it arose from there. It seemed so obvious that it was the right thing to do, but it took a lot of time to evolve and trust each other, which is a key issue.

■ What does your role as a coordinator of the UK CF Gene Therapy Consortium involve?

My role is making sure that everybody is working together as harmoniously and as efficiently as possible. That means two things: one is people trusting each other, and that takes time on the whole. The other is accepting that we probably will not work at better than 80% efficiency, and if you strive for complete perfection then you probably will not get that. You have to understand that this sort of model will never work 100% efficiently. My job is also to make sure the strategy is right, that people are working together well, and to spot the problems when they inevitably arise.

■ So how many projects are there usually going on at any one time within the Consortium?

We tend to work more like a small pharmaceutical company than a group of academics. Thus, we have a product pipeline and do not rely on one product to solve the problem.

In the Consortium we have product waves: our Wave 1 product is the one that is going into a clinical trial next year, and our Wave 2 product will probably be moving into clinical trials in around 4 years' time or so. So we have two big projects at any one time. However, within each of those there are numerous smaller projects. For instance, if you want to do a gene therapy trial next year, you need a project on recruiting the patients, you need a project identifying the best nebulizer and so on. There are several teams of people under the two main projects working on these. I oversee the Imperial College group and I coordinate the whole Consortium, so my job is to know about all the projects, coordinate and make sure things are going in the right way.

■ So what are the Wave 1 & Wave 2 products?

So the Wave 1 vector, the vehicle by which you transfer the gene into the cell,

is a fat molecule, a liposome, produced by Genzyme Corporation in Boston; we believe they produce the optional liposome; we have tried and tested many. We wrap the DNA with this liposome (called Lipid 67).

Interestingly, our Wave 2 product is actually a virus, known as a lentivirus. This seems to get into the lung extremely efficiently, and remarkably gives you expression of the protein for at least 2 years following a single administration. The other unique feature of this virus is that you can repeatedly administer it – we really do not know why. It is a very different virus to anything that we have handled before. Its surface contains specific proteins that make it 500-times more efficient than the liposome, it lasts for a very long time and can be repeated, so it is a very exciting product that has recently won The Medical Futures Respiratory Innovation Award 2011 and the MRC Best Translational Research Innovation Award 2011 in a national competition. The key thing with viruses is that you have to be very careful about the safety profile. This is the reason why it is not available to enter clinical trials right now.

■ **The Consortium is working towards a major new clinical trial. How will this differ from past clinical trials?**

There has never really been a long-term CF gene therapy clinical trial that has aimed to improve patients' long-term health. Giving a single dose of gene therapy that lasts 2–3 weeks will not improve lung disease in patients with a lifetime of having the condition. The only trials that we have carried out previously have been single application studies. Expression of the CFTR protein, regardless of how successful it is over a few weeks, will not be able to improve a patient's health long term. Past trials have simply been proof-of-concept studies, to test the concepts that you could put the gene in, and that the protein is made, and that you can measure the protein electrically. However, that does not tell you if the patient's lungs are getting any better.

The whole Consortium Wave 1 strategy is based on the idea that the gene therapy will have to be given repeatedly, and that it has to be given for long enough (in our view probably a year or so) to have any chance of getting the patient better. So, the Wave 1 project that we are putting into practice for next year, is to give a large number of patients (roughly 60 patients treated with the gene and roughly 60 with the placebo) monthly therapy for a year, and then measuring lung function and other parameters that assess if the patients are getting better.

One study in the USA by Targeted Genetics involved three monthly administrations of the adeno-associated virus (AAV) to see if theirs could improve lung function. It worked after 1 month, but not after 3 months. This may be because it is a viral vector and the patient builds up an immunity to it. Apart from that study, we are the only CF gene therapy study in the world that has looked for clinical benefit.

The Consortium has performed six trials with liposomes, but these were all single administration. We are excited to see if there will be a clinical improvement from multiple administrations in next year's trial using this vector.

■ **Will we ever circumvent the obstacles of viral vectors?**

Generally, the USA has been doing viral work and the UK has been doing nonviral work. The first paper was published in *Cell* in 1993 using an adenovirus and since then the USA has maintained very much a viral focus. Having stepped back and looked at it, we could not persuade ourselves that we could repeatedly administrator viral vectors. We have never seen a way of circumventing the obstacles of viruses until our lentivirus product. So, yes, it appears that it is possible to circumvent the obstacles of viral vectors.

■ **Currently, what is standing in the way of gene therapy, effectively, curing cystic fibrosis?**

I would prefer to avoid the word 'curing'. Not to be pedantic, but until we can deliver gene therapy to the lungs of a CF baby an hour after they are born, and therefore prevent any lung disease happening, curing is a different word. Generally speaking, at the moment gene therapy is going to be given at the time when people already have lung disease. Thus, at present we are hoping to stop it getting worse or improve it.

The other thing is that CF is a multi-organ disease; it involves the gut disease, pancreas, bones etc., and just by putting a gene in the lungs we are not going to alter any of those things.

The main obstacle is delivery. It is not a very complicated notion: we have got the gene, and we can spray it down into the lungs. If we can just guarantee putting it into the cell, I think we are there.

■ Do you think that CF will always be a disease that needs to be treated with several different approaches?

I am hoping not. In my lifetime I am hoping that we will improve lung disease in CF. Perhaps parents of children who are born this year, with the newborn screening program we have in the UK, will know within days whether their child has CF; then we could start gene therapy straight away and prevent any lung disease. I would then hope that they will not need any other lung therapeutics except gene therapy.

■ Is there a future for treatments that just alleviate CF symptoms?

I think that these products have done very well. Life expectancy has risen substantially, and that really has been because of antibiotics, good physiotherapy, mucolytics and so on. That field has done remarkably well, but I think now we need something that hits the basic defect and not just the symptoms.

The new CF potentiator compound, VX-770, is a very good example of hitting the basic defect. CFTR potentiators are ahead of gene therapy, and this is very exciting. Unfortunately, they are only suitable for about 4% of the world's CF population, because it is mutation-specific, whereas gene therapy is mutation-independent. Nevertheless, it is a good example to show that if you hit the chloride movement and improve it, that really does improve patient health.

■ Can you see CF potentiators for a wider scope of mutations coming about?

VX-770 potentiates the CFTR that is already there on the cell surface in 4% of patients; for the majority of the others, the protein is misfolded within the cytoplasm and what we ask a 'corrector' to do is correct the misfolded protein and let it fold properly so it reaches the cell surface. That may be beyond what science can achieve at the moment. Protein misfolding underlies many diseases, such as dementia, so it is very much a 'holy grail' if you can refold proteins. It would be very exciting if CFTR potentiators did compete with gene therapy, but I am not sure about the timelines for this.

■ What advances do you hope to see in gene therapy for CF in the next 5 years?

I really hope that our Wave 1 clinical trial, which should provide results in 2014, shows some degree of success. We are not assuming that this is going to be the answer. The aim of this trial is to assess the concept that if you give gene therapy repeatedly over a year, the patients' lung function will improve. Then I am hoping that the Wave 2 product, the lentivirus, will come through and that it will prove even more effective than the Wave 1 product. So, my hope for the next 5 years is that we begin to see some real clinical benefit. Up till now, no one has shown any individuals getting better with gene therapy, because nobody has done the studies yet.

This is a good time for gene therapy. It usually takes about 20 years to bring a product to market, and we are within 10–15 years; the Consortium has been going for 10 years, which means we are on the right time scale. People often say progress is going slowly, but it is not. It is a journey and we are going at about the right pace compared with other things. We would like to go as fast as possible, but we can only go as fast as science will allow us.

■ Funding must also be an important factor; is this slowing progress?

At the moment the economic situation has hit the CF Trust hard, and we have had virtually all of our funding withdrawn. This has really slowed things over the past year because we have spent the whole year not doing science or seeing patients, and just scrabbling around trying to find money. There is no question

that it has slowed us down by a year at least. Currently, we do not have any funding certainty to do the trial, but we are trying very hard. It helps that the Consortium is run like a pharmaceutical business. When we have been talking to pharma companies and figures in the business world, it helps that we have a fairly efficient model. I think we are beginning to recover, but we are going to have to look to other models of funding other than the current ones.

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