Interview Transcript - Dr Richard Harbottle

Hello, I'm Dr Sharon Ann Holgate and I'm here in the gene therapy research group in the section of molecular medicine at Imperial College London to talk to Dr Richard Harbottle, who's doing research into renal gene therapy in BHD syndrome, which is being funded by the Myrovlytis Trust.

My big interests were for my PhD, was how to get DNA or gene therapy vectors into cells. And so what we really wanted to do was try improve the DNA and the vectors we used for gene therapy. So we were working on gene therapy projects.

What BHD research are you currently working on?

Well, what we're trying to do is develop new vectors that can be applied to BHD. BHD is quite a complicated disease and the molecular mechanisms of it are complicated, but the gist of it is that the patient suffers from having two mutated copies of the gene that expresses folliculin. Perhaps they're born with one mutated copy and then they spontaneously mutate a second copy of it. And when the cells don't have folliculin or an active copy of this protein, then the cells go out of control and they form cysts or tumours. So our idea of using our vector system is to pre-treat these cells to put a third copy of the gene that encodes folliculin, which maybe will protect the cell from mutation and then subsequently the disease.

What factors have kept gene therapy away from being used as a treatment so far?

I think we were too ambitious in the beginning. I mean it's—gene therapy is a very new field. It's—when I did my PHD then, I started that in the early 90's. We worked in the cystic fibrosis field. Our research group grew out of searching for the gene that caused that disease and then we decided that we would try and cure it, so we were a cystic fibrosis gene therapy group. We had ambitions of making up a formulation in a tube with DNA which could replace the gene that was mutated, mixing it up with a gene delivery formula and then just inhaling it, like you might with an asthma puffer. But the lungs aren't designed like that, they prevent things from delivering DNA to the lungs. So the body's got lots of natural defences and we

didn't consider that the body would try and prevent us from trying to deliver DNA. So that's really been the biggest barrier—is efficient delivery and transfer of genetic therapy to cells.

What's the usual public response to gene therapy?

Quite often, in the early 90's, people were very excited and the charities were trumpeting gene therapy as the future of medical research. And I think everything came down to earth with a bump when the initial enthusiasm really gave way to a realism that we couldn't actually cure genetic disorders. Patients are very keen to know that people are researching their condition. It's probably soul-destroying if you've got a genetic disorder that there's no real treatment for that, there's no drug which can compensate for a mutation in your genes and one real way to do that would be to provide a new functional copy of the gene. And so, I think there's great enthusiasm there, but tempered with a bit of realism.

Are you working in collaboration with any other researchers or teams, either in the UK or internationally?

Well, I'm fortunate enough to be working quite closely with a group at the NIH in Washington and they're leaders in the field, they've worked on the molecular mechanisms of the disease, they've found the gene, and we're collaborating on some gene therapy projects with them.

What have you achieved so far with this research project?

We've managed to get our vectors to express folliculin. We can model this in cells. So we've got cells we've taken from a patient's tumour and we've managed to put folliculin back into these cells, and we can grow them and we can understand better what happens to these cells when they have a functional copy of folliculin again. And we hope to take the same vectors and then pre-treat cells to see and understand what happens if these cells are protected by a copy.

Has any of the research that you've been doing helped us understand more about the role of folliculin?

I think it will, because we can put folliculin back into cells which cause tumours, cells which have become a tumour, a tumorous cell, and we can also mark these with luciferase or another gene which allows us to track these cells. And what we can do is we can quantitate where the tumours are and we can tell the difference between a cell which is a tumour cell which has no folliculin and one which has folliculin and we can follow the pathway, quite simply.

So what's the ultimate aim of this research?

The ultimate aim would be to put as many back-up copies of folliculin into a patient's kidneys or lungs or skin cells, that even if they have the spontaneous mutations which manifest themselves throughout their lives, that these cells would not go on to form diseased cells and tumours and cysts. So it's a prophylactic gene therapy that we might be able to provide them to prevent the disease.

How does your delivery system for gene therapy differ to conventional methods?

Well, conventional methods are—and the most successful methods for gene therapy—are the ones that use viruses. The two diseases I talked about, for the immunodeficiency and the beta-thalassemia, they were treated by taking cells from the patient and injecting them with, or infecting these cells with a lentiviral vector and then putting the cells back into the patient afterwards. And although this vector system is very effective at delivering its DNA, the DNA integrates into the genomes, so the genomes themselves of the cells can be damaged. And if that's the case, then they can cause viral leukaemia afterwards. And, so using a virus, although very effective at gene therapy, there's also the disadvantages that viruses can cause disease and other damage, and our vector systems don't use that technology.

How could renal gene therapy potentially benefit people with BHD syndrome?

It's very difficult, because we don't want to modify their kidneys other than put in a better copy of folliculin. So our idea is to get the folliculin gene into as many renal cells as possible and then in principle those cells should not develop tumours whatever happens to the

genomic copy of folliculin and so ideally you'd protect as much of the patient's kidneys as you could.

How much more work do you think would need to be done before gene therapy could be an effective treatment for BHD and how long would you estimate this would take?

Well, we just started for a year doing—we're into our—beginning our second year of gene therapy project in BHD and we've already worked out really nice ways to deliver these DNA's to the kidney cells. And our intention is to do a pre-clinical trial with a group in Washington to test our model systems to see if we can get the gene and see how many cells we could protect with a gene therapy vector. So that's within one or two years and then I think we could scale this up and improve things; I mean our technology's improving all the time—our delivery systems and the DNA. So I think within a decade, we would have clinical application for gene therapy for this disease.

What other diseases or syndromes do you feel overlap with BHD? Do you feel your research is contributing to the understanding of these overlapping syndromes?

Well, VHL is a very similar disease; it's caused by a similar gene which is mutated in the patients, and not only do they get renal tumours they also get—there's many other conditions that are caused by this mutation. That's very similar so I see very simply that we could put the VHL gene into our plasmids and introduce them into the kidneys and the kidney cells in the same way, and if it works for BHD then there's absolutely no reason why it wouldn't work for VHL.

Where have you presented your research so far?

I've presented some of it at the gene therapy meetings and the background for this has been presented in the British Society for Gene Therapy and the American Society for Gene Therapy. But I was fortunate enough to go over to Washington earlier this year and I attended the BHD conference and afterwards I visited the lab at the NIH and I presented my work there to the surgeons who are actually dealing with patients with BHD. And it was very, it was gratifying to know they were excited about the work we were doing.

How do you think the BHD research field will look in five to ten years' time?

Well, if you think about the last five to ten years there's been great development in [the] understanding of the disease and they know the mechanisms of it. I mean it does a complex cellular effect and losing a protein like folliculin can cause all sorts of things to go wrong with the cell, and we're beginning to understand that better, and surgery's improved certainly; and that's the biggest way to tackle BHD, certainly with renal tumours—is to remove them surgically. But the application with gene therapy certainly will help all of these efforts and then the molecular modelling of cells and tissues using the vectors that we're developing will allow better understanding of the effects of the genes and the replacement of the genes, but we also might be able to develop this therapeutic too.

Thanks ever so much for talking with me today Richard, and best of luck with your research for the future.

Thank you. You're welcome.