Announcer:

Welcome to the Eye on the Cure podcast, the podcast about winning the fight against retinal disease from the Foundation Fighting Blindness.

Ben Shaberman:

Welcome everyone to the Eye on the Cure podcast. I'm your host Ben Shaberman with the Foundation Fighting Blindness, and I'm delighted to kick off the new year with Dr. Robert MacLaren as my guest. And Dr. MacLaren is a world renowned retinal surgeon and clinical research, and he's been on the forefront of gene therapy development for retinal degenerative diseases.

Dr. MacLaren has been a lead or co-investigator on several clinical trials for retinal gene therapies, including those for RPE65, associated LCA, choroideremia, X-linked retinitis pigmentosa and age-related macular degeneration. And he was also a lead investigator for an artificial retina or retinal prosthesis, as we often call it, developed by a German company called Retina Implant AG.

Finally, I wanted to mention that in 2016, he conducted the first robotic eye surgery on a human, and we'll be talking about that a little later. So Dr. MacLaren, it's an honor and a pleasure to have you on the podcast.

Dr. Robert MacLaren:

Thank you very much indeed, Ben, for the kind invitation.

Ben Shaberman:

So a little more on Dr. MacLaren, just to give you a little idea of what his day-to-day activities are like. He has many. He is professor of Ophthalmology at the University of Oxford, a consultant ophthalmologist at the Oxford Eye Hospital. He's an honorary professor of ophthalmology at the University College London Institute of Ophthalmology. He's an honorary consultant, vitreo retinal surgeon at Moorfield's Eye Hospital. And also very importantly, he leads the Retinal Research Lab at the Nuffield Department of Clinical Neurosciences at Oxford.

A little bit on Dr. MacLaren's education, he has a bachelor of medicine and bachelor of surgery from the University of Edinburgh Medical School. And those bachelor degrees are kind of like our doctorate degrees here in the U.S. He also has a doctorate, like a PhD, in optic nerve regeneration from the University of Oxford. So lots of great experience and credentials. Very exciting to have you on the podcast.

But to begin, I'd like to have you tell our listeners what drew you to the eye and the retina and what inspired you to become a surgeon along with that?

Dr. Robert MacLaren:

Well, thank you indeed, Ben. That is of course a very perceptive question. When I went to medical school, I always felt that my practical skills were better than my intellectual skills. And for that reason I had in mind a surgical path and I enjoy the creativity of doing things with your hands. The background further is that my father was a photographer and I used to accompany him a lot on photographic trips and I worked in his darkroom and learned a lot about cameras and optics.

So when I specialized in surgery at the very beginning during my medical school career, I was naturally attracted to the concept of eye surgery because I had already prepared myself a lot to understand the eye and how it worked. And I think it was in my second year at medical school when I was able to use the ophthalmoscope for the first time to see the back of the eye and I could see in all its beauty, the

blood vessels, the nerves, everything there, clear and precise and it really did appeal to me. And from that day on, I decided to have my career going forward to be an eye surgeon and I'm very pleased that I managed to meet that goal.

Ben Shaberman:

That's a great story, especially about your dad. Do you find it challenging doing such delicate surgery? That's what seems impressive to me is how you have to be as a retinal surgeon, not that other surgeries, you don't have to be that careful, but the retina is so fragile and so small.

Dr. Robert MacLaren:

I think you're right, and I often talk about this with medical students. When I was a schoolboy, very early before the age of 10 years old, I used to spend a lot of time painting tiny toy models like toy soldiers. And although one can't practice as an eye surgeon in childhood, as if for instance, if you're a tennis player, you might play tennis from an early age.

If you're someone who basically has been doing very fine motor skills from early time in your childhood, it's likely that you will have ingrained in your brain and those networks, the ability to make microscopic movements, which is then something that you can translate into an eye operation when looking down the microscope. And indeed, I was using optics to see what I was doing when I was painting these very tiny soldiers and figures in great detail in my early childhood.

Ben Shaberman:

That's really interesting. I remember those days when we were kids painting models. I don't know if anybody does that anymore, but that's interesting that you were able to translate that skill into surgical skill. Very cool. So it's one thing to do surgery, but it's yet quite another to do research and development of therapies. Were you always drawn to research and working on emerging therapies?

Dr. Robert MacLaren:

I think it's very easy to think about being a clinician and doing research as separate independent entities. I'm very much of the opinion that if we're treating our patients, we are using techniques, equipment, ideas that are being developed and proven by physicians and surgeons in bygone years. And it is our duty to try and push the field forward and try and develop new treatments.

So I think the research in itself is just an extension of being a good clinician because when you see lots of diseases, you recognize patterns, you can then think about treatment modalities in a way that be extremely difficult for a commercial scientist or academic scientist who doesn't work in the field of ophthalmology. And I always encourage my colleagues to think a little bit to do that themselves.

Of course, one can start doing research by working with commercial organizations running clinical trials. And at the other end you can get involved doing lab work as I do and doing work and the research of your own. It is possible, and I think it's a very important part of the work that we do as clinicians.

Ben Shaberman:

And you were talking about therapy development as an extension of your clinical practice. With inherited retinal diseases, there's such a huge unmet need that I can see how therapy development is such a natural extension because you want to help those patients. Again, the need is huge.

So one area of therapy development, really the area that you've been involved with most, is gene therapy. And we'll spend quite a bit of time talking about gene therapy. But for our listeners, can you give them just a quick definition, maybe a few sentences to explain exactly what gene therapy is?

Dr. Robert MacLaren:

Gene therapy is, broadly speaking, a medical treatment technique where you try and correct the disease by using genetic material rather than classic pills that you might take by mouth or injections. And that genetic material could be DNA or it could be RNA.

And as you may recall, the DNA is a genetic code on your cells that is on your chromosomes. And the RNA is a little bit of reading material that comes off the DNA to make a specific protein. The great advantage of gene therapy is that you can be very targeted with a specific gene and also you can use a viral vector, which is a means of delivering the DNA into a cell. And that can be very specific.

For instance, if you have inflammation in the eye, for instance, and you take a steroid pill, that pill is going to affect every single cell in your body. It's going to be absorbed, it's going to be in your blood everywhere. A relatively small proportion will go into the eye. But if you can deliver a gene therapy treatment into the retina, into the eye, you can obvious then treat the cells directly.

And for that reason, I'm firmly of the opinion that gene therapy will take over in future and replace a lot of the work we're doing at the moment with injections into the eyes and giving patients pills by mouth.

Ben Shaberman:

Great explanation. And the eye, the retina especially, are such good targets because they're small and so easily accessible. So the gene therapy for the retina got off the ground in earnest somewhere in the neighborhood of 15 years ago, especially with those early trials for RPE65, and ultimately Luxturna. The first regulatory approved gene therapy became available about a dozen years later, 10 years later.

Since the advent of that clinical trial in 2007, 2008, we've had a lot of great advancements. There's a lot of great activity. There have been some successes, but there have also been challenges. And I guess this is a big question, but where do you feel the field of gene therapy is at now? What have we accomplished and what do we need to do to advance the field even forward and get more therapies out to patients?

Dr. Robert MacLaren:

Well, I don't know how long this podcast is, but on the second point, we could be here 24 hours if you want. So I'll try and summarize it a bit. Let's not forget that we do have an approved treatment in gene therapy and in the UK that was the first one to be approved. The National Health Service approved Luxturna.

I should obviously acknowledge that the background work to that was led by mainly Jean Bennett and Al McGuire in the United States. And that work over 10 years or more led to the approval, and nowadays, my residents just seem to think it's a normal thing and they don't appreciate the huge amount of work that went into getting us up that first step. Because clearly now that we have one approved treatment, it's going to be much easier to get other treatments approved because we've established the principle that gene therapy, using the adeno-associated viral vector is effective in treating genetic diseases affecting the eye.

And ideally, we want to go in and intervene as early as possible. There is no point really treating a retinal degeneration when there's only 1% of cells remaining. You'll get a response, sure. But ideally you want to preserve as many cells as possible. And I think as we understand more about gene therapy, we are in

a position now where we can be more confident in going in earlier with earlier interventions because we're more aware of the side effects.

Now, this leads me on to another important point is that when we think about gene therapy and we think about developing these very exciting viral vectors in the lab, it's important to remember that at some point we need to inject it under the retina in a patient. And so in parallel with developing the gene therapy molecular biology, I've already been working with my team in Oxford and colleagues elsewhere to improve the success of the surgery, to make the surgery safer.

And I was at a meeting in Rome a couple of weeks ago, a whole session on subretinal gene therapy, with leading surgeons from all around the world now established with the technique talking about little nuances. Whereas when I started out in this over 10 years ago, if I stood up and told an audience of ophthalmologists that I'd be detaching the retina to inject a virus underneath it, they would almost have called security to have me evicted thinking I was some kind of crazy guy. So we've moved a lot, but I mentioned this because it's important to remember that we need to develop the surgery to deliver the vector at the same time as developing these interesting technologies.

Ben Shaberman:

And that's a very important element of getting a gene therapy to a patient, and I don't think we appreciate that enough. Can you talk about how you've used robotics to improve potentially the outcome of surgery to the retina?

Dr. Robert MacLaren:

Absolutely. I was at the European Retina Society meeting, I [inaudible 00:12:30] at a Euretina meeting a few years ago, and I think it must have been around about 2014. And I was pleased to have received an award at that symposium. But I came second to Mark de Smet, who won the main award of the meeting for his work on developing this robotic system.

And effectively what it is, it's an arm that moves up and down and moves precisely with eight independent motors and it's remotely controlled, and effectively it takes over one of the hands of the surgeon when doing an operation inside the eye. So, I had a chat with Mark and we discussed things. Subsequently, it became apparent to me that what we want to do in gene therapy is we want to detach the retina extremely slowly and we want to do it as still as possible because every time you move the needle in the eye slightly, if the needle has penetrated the retina to inject the virus, then it'll make the whole little bit bigger.

The result of that would be the leakage of virus coming back from the subretinal space into the vitreous, which as we know will cause significant inflammation. So subsequent to the meeting, I contacted Mark and his robotics team in Eindhoven, and we agreed to work together on the robot to see if we could find a way of actually using it to do injections under the retina.

Now, at the time, the robot had never been used at all in the human.So before going to the Ethics committee and doing something really exciting, like using a robot to do gene therapy, in other words, an unknown use for an unknown device in an unknown therapy, we set up the trial so that I would do the operation that is relatively straightforward that could be taken over manually if the robot failed.

So, our first study was to look at doing epiretinal membrane peels and ILM peels in treating membranes and macular holes, and we did it properly. We had 12 patients. We randomized them to the manual surgery, traditional surgery or the robot surgery. And I'm pleased to say that that trial was a huge success. The robot wasn't any quicker than the manual treatment, but it was just as safe, and this was the most important thing. It was a safety study.

Of course, the plan was then to use the robot for subretinal injections. And we subsequently did another follow-on study for the injections. And that was published in the AGO last year, I think, using it to inject TPA, which is a clot lysis product for dissolving blood clots in patients who have macular degeneration to displace the hemorrhage. And again, that was a very successful trial.

And we're currently working on doing the final finishing that touches the robotic surgery to bring it into clinical trial now for doing gene therapy treatments. And I should point out that it's very exciting research. The robot has a huge advantage in that you can have complete control of the operation. We can advance the robot 50 microns at a time and it's completely still inside the eye. That means we can slow the infusion down.

If you slow down the infusion, you're going to get a lot less stretching of the retina, which is going to cause less damage in the thin retina and basically make the whole process much, much safer. So that's currently where we are, and also developing it for other exciting technologies of injecting things into the eye. I'm pretty sure that you'll hear more about that over the next year or so.

Ben Shaberman:

That's so exciting. We greatly appreciate those advancements because as we've alluded to already, that surgery is so delicate, so to come up with technology that can do it even more safely is wonderful.

To get back to the gene therapy advancement, the work we're doing to get more gene therapies across the finish line, in some of the recent clinical trials, we've had nice evidence of efficacy. But we've also had challenges meeting the end point of the trial, the outcome measure that the regulators need to actually approve the therapy. How do you see the field moving forward so in these trials, we can actually get more therapies across the finish line?

Dr. Robert MacLaren:

Well, that's a very interesting point, and again, we could talk a lot about, this is a constant question that we're being asked. So one of the problems we have is that the regulators set the bar very high. Now, that's a good thing. Of course, we always want safety, but if the bar is set so high that it's no longer commercially viable for a company to market a product and run a trial for a rare disease in which there are very few patients at the end that are going to be treated, then we are running into problems.

I think they need to be a little bit more aware of how difficult it is for the companies and how expensive it is. To give you an example, there is a huge emphasis on testing of drug release products for the gene therapy vectors, which is quite onerous. And on top of that, we have the European Medicines Agency and the FDA, which are the two main regulators for Europe and US and elsewhere. So at the moment, both of them require independent testing of the drug product and drug substance before they approve it in their country, which is going to take hundreds of vials.

It's just simple things like if we could just get them to agree on the standards together, we would only need to go through the process once rather than twice. We possibly could only have one trial rather than two, and we could increase the end numbers, and therefore, we could achieve the end points with a fewer number of patients in total, including both US and the European Union, or Europe, and I include the UK in that.

We're all members of NATO. We've agreed on standards to go to war together, and it is a great shame that we can't get our regulatory authorities to agree because this is really a big cost. And to make matters even more confusing, the regulators want different endpoints. So the European Medicines Agency is happy with the two-line gainer vision. The FDA would like to have a three-line gainer vision.

The European Medicines Agency is not very keen on having a low dose as in addition to the control and the therapeutic dose; the FDA wants to have a low dose and a high dose as well as a control.

So if they could just get together and have a discussion and agree on a common framework that would exist on both sides of the Atlantic, that would again reduce the trial costs considerably, which would help encourage the companies to keep the course with the rare diseases. Knowing that their costs of running the trials would be lower and the chance of meeting the end point would be greater.

So, this I think is where I think we need to give a bit more guidance for the regulators to try and get them to see it from our perspective. Because the reason that the trials are not successful is not necessarily because they haven't met the end point in terms of the clinical result to the therapy. It may be issues around the manufacturing and maybe other issues around the cost. That means the companies are not really keen to push it and argue the case with the regulators.

Ben Shaberman:

Well, thank you for elucidating that need to educate the regulators and have them collaborate and work together. And I know at The Foundation Fighting Blindness, we're working to make that happen as well.

So Dr. MacLaren, to close out our discussion, I know you run a really innovative research lab at University of Oxford, and you're coming up with all kinds of new therapies and approaches to therapies. Can you talk about, perhaps give an example or two, of what you're working on and what you're excited about?

Dr. Robert MacLaren:

Yeah. We have basically, I guess, three main areas of research. I have a clinical research program where we have research optometrists or incredibly talented people looking at these end points, looking at the reproducibility of testing, look at reliable measurements of visual function in patients with rare diseases.

Because we've got clinics in Oxford full of these patient rare diseases, there's a lot of patients they can look at. And so that's very, very helpful and that helps us inform companies and regulators and others on what sort of end points might be helpful and reliable. We also have a program where we're actually doing the basic science in the lab. I have anywhere between six and eight PhD students, five postdocs, additional scientists, visiting clinicians and visiting research scientists. And we're all working on gene therapy programs.

When I started the program here in Oxford over 10 years ago, we were looking at gene replacement therapy to try and tick off the most common retinal diseases that we could simply replace the gene with. But we are pretty much done that now, particularly since we've seen the huge successful results with our x-linked retinitis pigmentosa gene therapy trial. So we are now moving on to look at ways of dealing with the larger genes and the dominant genes. And of course all of that is CRISPR and gene editing.

So everyone in my lab is working on CRISPR therapies and we are using the platform of the AAV to deliver the gene editing proteins into the retina to make the necessary corrections and edits. And we're going some fantastic results there again, which we'll be announcing in due course on the CRISPR therapies.

The third part of our research is really working with the companies in the clinical trials of the products that we've been involved with. And for that reason, we're working very closely with the new company, Beacon Therapeutics, which is a new company based based in Boston, which has got the assets of the IP from Oxford combined with the assets of AGTC, which has got a fantastic manufacturing facility. So we're working with them and again, guiding them with a clinical trial, training surgeons, identifying sites

around the world where patients might be selected, informing people on how to run clinical trials, all this sort of thing, which is really a great benefit in us getting the product approved.

So you can see if you like, there's a conveyor belt, and I haven't to put the boxes in the correct order on the conveyor belt, but just to reiterate, the first box would be to develop a new technology in the lab and then to show it works maybe in an animal model. Second would be to look at patients with that disease, identify the end points, and basically give the company the information they would need to say, "This is how you design a clinical trial. This is a number of patients around, this is where the patients are located, these are the end points that you're going to get and this is how you're going to get it approved." And then the third part of that equation is to engage with industry and raise the funding, the commercial funding, the venture capital funding, to support that clinical trial going into phase three and beyond to get the product approved.

So it is not enough. I say to my colleagues, "It's not enough to do exciting research in the lab and get your Nature medicine paper and then start something else. It's up to us as clinicians, as clinical scientists, to go beyond just the proof of principle and the great science in the Nature medicine paper and then go on and run the clinical trial and get the commercial funding and put it back into the clinical domain." Because as clinical experts, we are the ones that can help guide the commercial people. It is very difficult for them to do that by themselves. So, that's the vision I have.

And the vision I think has been for me quite clear, but you need a bit of a vision because there are a lot of setbacks on the path, but sometimes I can take myself forwards in time and imagine I have an approved treatment or disease, what am I going to do to get that treatment approved? And then look back at the hoops that one needs to jump through to get to that point.

It'd a bit like you can go up to the summit of Mount Everest and look down and you can see more clearly the root to the top than you can sometimes when you're sitting at the bottom covered in snow and cloud with not much visibility. So I think that's a great asset we have as clinicians when we do laboratory research, we can see the direction it needs to go in, and we can use our clinical acumen to understand a lot more the basic principles of the diseases we're trying to treat.

Ben Shaberman:

So eloquently put, and you've had a lot of success in that endeavor over the last several years, and I think I can say for our listeners, we're so grateful that you continue to move forward in clinical development of therapies because it is so challenging, as you've just said. We need the pioneers and the soldiers on the front line like you to move these therapies forward.

It isn't easy. You just can't show efficacy in a mouse or an animal and then check the box. That's just really the first part of the challenge. And again, we appreciate the great work you're doing on the clinical trial front lines.

Dr. MacLaren, this has been very enjoyable, very insightful. This conversation has been a great way to kick off 2024, and I greatly appreciate you taking time out of your day to give us your great insights and experiences.

Dr. Robert MacLaren:

And thank you very much indeed for giving the opportunity to speak. And I would say to all of your listeners, please don't give up hope. We're all working very hard behind the scenes to find a cure.

Ben Shaberman:

Thanks for saying that, and again, we're glad to have you driving that hope. And listeners, happy New Year to you all. It's always great to have you on the podcast, and we look forward to having you back again soon.

Announcer:

This has been Eye on the Cure to help us win the fight, please donate at Foundationfightingblindness.org.