Interview

Stemming vision loss with stem cells: seeing is believing

Professor Coffey joined the faculty at the University of Oxford in 1987 on completing his doctoral work. In 1989, he was awarded a personal Royal Society Research Fellowship, at the same time moving to the University of Sheffield to establish a new laboratory for retinal transplantation. After 14 years at the University of Sheffield, Prof. Coffey was appointed Professor in the newly built Henry Wellcome building for translational eye research at the Institute of Ophthalmology in London. Prof. Coffey has many years experience in cellular therapies as applied to retinal transplantation and was recently the principal author and co-author of two landmark papers demonstrating that grafting human cells could prevent visual loss. As Professor and head of Ocular Biology and Therapeutics, Prof. Coffey has established the London Project to Cure Blindness. This project aims to deliver a stem cell therapy for age-related macular degeneration by 2011.

■ What first led you to focus your research on cell therapies for age-related macular degeneration in the late 1990s?

To give a little background on age-related macular degeneration (AMD), the disease tends to occur in a population over the age of 65 years. Typically 25% of this population suffer from some form of AMD. Still-unknown mechanisms cause the support cells in the back of the eye (the retinal pigment epithelium [RPE] cells) to dysfunction, specifically in the area of the central visual center, the macula. Consequently, debris builds up in these cells and deposits known as drusen form in the area where the cells at the back of the eye have started to deteriorate. Over a period of time the RPE cells start to die. Therefore, the seeing part of the eye, the neural retina, no longer has support from those cells and the patient goes blind.

The major reason for looking at a cell therapy for AMD is that it is this single cell type that degenerates and dies as a consequence of the disease and, therefore, we thought this was a perfect example of how we could look at a cell therapy to replace those cells that have been lost through the disease.

■ What current treatments are available for AMD and what are their shortcomings?

There are two forms of AMD: wet and dry. The largest population is the dry form and at the moment there are no therapies that

can be given to these patients. Lifestyle changes and dietary supplements have shown some help in slowing the disease and there are some agents coming onto the market that may continue to slow the progression of the disease, but these are still very much in their infancy.

The smaller population of patients with wet AMD can be treated. The reason it is called wet AMD is that leaky blood vessels grow through that layer of support cells, and blood is leaked between the neural retina and the RPE, pushing the neural retina away from its support. Fortunately, in those patients there is a new class of agents that stop the bleed, the anti-angiogenics, derived from therapeutics used in cancer. The introduction of these drugs has shown some outstanding results: up to 30% of patients treated have a significant improvement in vision. The problem with the anti-angiogenics is that they have to be injected into the back of the eye every 4–6 weeks for the rest of the life of that patient. In addition, the drugs are quite expensive, approximately £1000–1500 per treatment in the UK.

Given the lack of treatments for dry AMD, and the time-consuming and expensive nature of treatment for wet AMD, the market for a cell-based therapy is large. Looking at wet AMD, the anti-angiogenic drugs are a billion dollar market. In the UK, for example, there are approximately 0.5 million patients in the advanced stages of AMD. In total in Europe, 14 million people have some

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form of AMD, with an equal number in the USA. It is a very large clinical population.

■ What has been achieved to date by the London Project to Cure Blindness?

The concept behind the London Project to Cure Blindness was to take a cell therapy as safely and quickly as possible into the clinic. The project was established in 2007 and looked at how we could drive a cell therapy forward to treat a disease such as AMD. We have now produced a cell bank from a human embryonic stem (hES) cell line, which we can then turn into the appropriate cells that we need: the RPE cells. We are producing the cells to clinical-grade standard, so we can carry out further tests. We have grown the cells into single-cell-layer carpets suitable for transplantation and placed them into animal models of retinal disease. We have also been able to use a large-animal model to try the full procedure as we would do it in a patient.

The next steps are to join with the regulators to establish what other information and safety data would be needed to allow us to go into early clinical trials. At the moment we are talking with the various regulatory organizations in the UK, the Medicines and Healthcare products Regulatory Agency and Gene Therapy Advisory Council, to ensure safety and compliance going into the clinical trial.

■ Is the project on track to meet its target of bringing a cell therapy for AMD into the clinic within 5 years?

I think we are definitely on track for the 5-year target. We do not know exactly what data the regulators may request, but we have done most of the preclinical work that we anticipate that we would need to do, and we hope that can go forward successfully.

■ Given the rapid advance of induced pluripotent stem (iPS) cell technology, do you anticipate iPS cells impacting on your work?

At the moment the hES cells are by far the most advanced towards the clinic for this application. We are working quite extensively on iPS cells and differentiating those

to RPE cells, and we presented some of this work at a recent international conference. But that is much further down the road.

There is still a lot to be done to understand whether iPS cells could be used as a therapy in AMD. There are issues around producing an iPS cell from an aged person, as it is uncertain whether they would be appropriate to replace back into the eye. The process of deriving iPS cells would have to be done for each individual patient, which, given the size of the AMD population, may not be feasible or cost effective. There are genetic components that are known to be a problem in AMD and it is unclear how far back iPS cells are reprogrammed: might the cells retain these mutations? There are still many questions to be addressed.

An area in which iPS cells could definitely be of value is as a disease pathogenesis model. That would be a very interesting avenue of research.

■ University College London recently announced a collaboration with Pfizer Regenerative Medicine to advance research into hES cell-derived therapy for AMD. How will the collaboration contribute to the project?

It is truly a partnership. Pfizer have extensive experience of working with stem cells, having been working in this area for a number of years now. They can contribute great experience in ensuring that the process towards the clinic is highly examined, regulated and scaled up. The collaboration ensures that both partners learn how to take a stem cell therapy to the clinic. Pharma will, for the first time, get a real indication of what has to be done to get a cell therapy towards a clinical application. Hopefully, if this is successful, they will be able to scale this up as a therapeutic that can be distributed to large numbers of patients.

■ Do you see this collaboration as a sign that big pharma are ready to start investing in regenerative medicine on a large scale?

Yes, without a doubt. I think that this is a real stamp of approval from one of the world's leading pharmaceutical companies,

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and a sure sign that regenerative medicine is now being taken seriously as a therapeutic.

■ **What other projects will you be working on over the next few years?**

If this cell therapy works for AMD then it could potentially be used for other conditions that involve the RPE, such as inherited macular dystrophies, which are caused by a genetic defect and tend to affect people of a younger age (early 40s).

I do have another project, looking at potentially the largest cause of blindness in the working population: diabetic

retinopathy. Rather than the RPE, it is the vasculature that is affected in diabetic retinopathy, but we hope to use a similar cell therapy approach to remodel the vasculature and restore sight.

Financial & competing interests disclosure

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