Review

Report for the trustees of Royal Blind on behalf of the Ophthalmology sub-committee of the Royal College of Surgeons of Edinburgh

Changing lives since 1505
Gene therapy 'could be used to treat blindness'

By Palleb Ghosh
Science correspondent, BBC News

16 January 2014

Surgeons in Oxford have used a gene therapy technique to improve the vision of six patients who would otherwise have gone blind.
Over nearly a decade the Royal Blind has donated between £150,000 to £250,000 in research grants each year to fund research in eye disease. This funding stream is administered by the Ophthalmology committee of the Royal College of Surgeons of Edinburgh. The Committee is chaired by Professor Stephen Wigmore of the University of Edinburgh and includes a panel of experts in eye disease from across the United Kingdom. Mark O’Donnell the Chief Executive of Royal Blind also sits on the committee. The funding that the Royal Blind provides supports fundamental research in eye disease as well as clinical research. The committee are always interested in assessing how the donations from the Royal Blind can be multiplied to generate even greater research support through the award of other grants and how research in eye disease can be translated into clinical advances for the benefit of patients. The Ophthalmology sub-committee of the Royal College of Surgeons of Edinburgh greatly value our association with Royal Blind and we have prepared this short document to show examples to the trustees of the great work they are supporting.

**Professor Stephen J Wigmore**  
Chair Ophthalmology sub-committee  
Royal College of Surgeons of Edinburgh
Development of gene therapies for treatment of blindness

Professor Robert MacLaren, University of Oxford

Background
Most incurable forms of blindness are due to genetic diseases which are caused by faulty genes in the cells in a region of the eye called the retina. The retina is the light-sensitive layer (like a camera film) that lines the back of the eye, and which allows us to see. These defective genes eventually lead to the dysfunction and death of the affected cells. The progressive death of these cells causes a gradual degeneration of the retina, resulting in sight loss and ultimately blindness.

Up until now, genetic eye diseases have been incurable. However, through the generous support of Royal Blind and the Royal College of Surgeons of Edinburgh, we have developed a new technique of gene therapy which we believe may help to slow or even stop the degeneration. The new technique involves putting normal copies of the affected gene back into the cells of the retina to help them to function normally. This is achieved by an operation to inject the normal genes into the retina, using a modified virus to carry the genes into the cells.

In gene therapy, we use a small viral particle known as adeno associated virus, or AAV, to carry normal genes into the retinal cells. This viral particle is not associated with any disease in humans. The virus survives by remaining dormant and undetected by the immune system. The ability of the virus to evade the immune system is very helpful because the lack of inflammation means that the virus does not damage the retina when injected into the eye.
Changing lives since 1505
Initial research grant funding by Royal Blind and the Royal College of Surgeons of Edinburgh

With the help of Major Ophthalmology Grants received from Royal Blind and the Royal College of Surgeons of Edinburgh awarded in 2008-2010\(^1\) \(^2\) \(^3\) we commenced the development of special AAV-mediated gene therapies for treatment of choroideremia and X-linked retinitis pigmentosa (XLRP), incurable genetic diseases that cause blindness in men. Sight loss in choroideremia and XLRP begins with ‘night blindness’ (i.e. loss of night vision) in adolescence, followed by a gradual loss of peripheral vision which results in progressively worsening ‘tunnel vision’, and ultimately complete blindness.

Major Ophthalmology Grants subsequently received from Royal Blind and the Royal College of Surgeons of Edinburgh in 2011\(^4\) and 2012\(^5\) enabled us to commence work on developing an AAV-mediated gene therapy for treatment of Stargardt disease, the most common form of macular degeneration in young people. Stargardt disease is particularly tragic as afflicted individuals start losing their central vision from the onset of the disease, meaning that they are soon unable to read a book or watch television, or even to recognise faces.

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\(^1\) £40,000 awarded in 2008 for the project ‘Developing gene therapy for cone neuroprotection in rod cone dystrophies’.

\(^2\) £45,000 awarded in 2009 for the project ‘Testing clinical treatments that might preserve cones in retinitis pigmentosa’.

\(^3\) £45,000 awarded in 2010 for the project ‘Development of in vivo retinal imaging to assess vectors for gene therapy clinical trials’.

\(^4\) £50,000 awarded in 2011 for the project ‘Preclinical testing of a new gene therapy vector for Stargardt Disease’.

\(^5\) £50,000 awarded in 2012 for the project ‘Optimisation of ABCA4 gene expression as a treatment for Stargardt Disease’.
We were awarded an MRC Developmental Pathway Funding Scheme Award in 2013 to continue our research.
Subsequent research grant funding and initial Phase 1/2 clinical trials

The promising results from our initial research enabled us to obtain significant funding in 20106 from the Wellcome Trust and Department of Health, to commence a Phase 1 clinical trial7 to test our AAV-mediated gene therapy for choroideremia. The promising early data, published in the Lancet in 20148, led to an NIHR Efficacy and Mechanism Evaluation (EME) Award in 20159 to fund a Phase 2 choroideremia gene therapy trial.10

We were also able to continue our research into the development of a gene therapy for XLRP through an MRC Clinical Research Training Fellowship awarded in 201211. This research was particularly challenging as the affected gene has an unusual genetic code that makes it very unstable and prone to mutations, which is why XLRP is one of the more common hereditary retinal diseases. However, as described in a paper published in Molecular Therapy in 201712, we were able to reprogramme the genetic code of the gene concerned to make it more stable, but in a way that did not affect its function.

Concurrently with the above, we were awarded an MRC Developmental Pathway Funding Scheme Award in 201313 to continue our research into the development of a novel dual AAV-mediated gene therapy for Stargardt disease. As the gene affected in Stargardt disease is very large and is therefore too big to fit into AAV particles, we developed an innovative solution to this problem which involved splitting the original gene into two gene fragments having overlapping segments, each carried by a different AAV particle, followed by recombination of the gene fragments into the original gene within the retinal cells. This work was described in a paper published in Human Gene Therapy in 201814.

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6 £1.2 million awarded in 2010 for the project ‘Gene therapy for blindness caused by choroideraemia – a Phase I clinical trial’.
9 £1.6 million awarded in 2015 for the project ‘Gene therapy for choroideremia – a Phase II clinical trial’.
10 ClinicalTrials.gov NCT02407678 ‘REPI Gene Replacement Therapy for Choroideremia (REGENERATE)’. http://clinicaltrials.gov/ct2/show/NCT02407678
11 £277,000 awarded in 2013 for the project ‘RPGR gene replacement in a mouse model of X-linked retinitis pigmentosa’.
13 £560,000 awarded in 2013 for the project ‘Developing gene therapy to treat blindness caused by Stargardt Disease’.
Spinout of Nightstar Therapeutics and the development of the international clinical trial programme

Following the positive outcomes observed in many of the patients in the Phase 1 choroideremia gene therapy trial, a gene therapy company (Nightstar) was spun out of our research programme in 2014, supported by substantial venture capital funding from the Wellcome Trust (through Syncona, formerly the investment arm of the Wellcome Trust). This enabled us to commence a Phase 1/2 clinical trial in 2017\(^5\) to test our AAV-mediated gene therapy for XLRP, followed by an international Phase 3 clinical trial of our choroideremia gene therapy in 2018\(^6\). This Phase 3 clinical trial, which will be recruiting 140 participants in 6 countries, is the largest gene therapy trial in the world to date. Following the publication of the successful results of the initial Phase 1 study in Nature Medicine in 2018\(^7\), we look forward to the successful outcomes of the Phase 3 study, and the eventual regulatory approval of the choroideremia gene therapy.

We remain extremely grateful to Royal Blind and to the Royal College of Surgeons of Edinburgh for their long-standing support, which has enabled us to pursue a highly successful translational research programme developing novel gene therapies for the treatment of previously incurable forms of blindness.

\(^{15}\) ClinicalTrials.gov NCT03116113 ‘A Clinical Trial of Retinal Gene Therapy for X-linked Retinitis Pigmentosa [XIRIUS]’. http://clinicaltrials.gov/ct2/show/NCT03116113

\(^{16}\) ClinicalTrials.gov NCT03496012 ‘Efficacy and Safety of AAV2-REP1 for the Treatment of Choroideremia (STAR)’. http://clinicaltrials.gov/ct2/show/NCT03496012

Gene therapy reverses sight loss and is long-lasting

By Pallab Ghosh
Science correspondent, BBC News

28 April 2016

A life transformed: Joe Pepper was slowly going blind until a gene therapy reversed his sight loss.

A genetic therapy has improved the vision of patients who would otherwise have gone blind.

A clinical study by British scientists has shown that the improvement is long-lasting and so the therapy is suitable to be offered as a treatment.
Improving visual function after treatment for retinal detachment

Professor David Yorkston, University of Glasgow

The PostRD study has successfully completed the clinical phase of the research. Over 300 patients were recruited. The aim of the study is to find out if it is possible to improve visual function after successful treatment of a retinal detachment. We have learned that when a retina is re-attached, it shifts a little. Occasionally the retina shifts so much it leads to a wrinkle in the retina, called a retinal fold. This shift can cause annoying symptoms of distortion, or even double vision. This may lead to difficulties in everyday life with activities such as driving or reading. The PostRD trial set out to determine if positioning the patient in a prone position, immediately after surgery, reduces the amount of retinal shift. The analysis is not yet complete, but it appears that it does not make a lot of difference to smaller degrees of retinal shift, and there does not appear to be any difference in final vision between those people who were face down immediately, and those who adopted other positions. However, the study did show that immediate face down positioning reduced the risk of retinal folds, the most severe form of retinal shift. For this reason, we expect that immediate face-down positioning is likely to be accepted as the standard of care for retinal detachments treated with a gas bubble in the eye.
This has led us to modify our practise in NHS Lothian: people now have retinal eye screening on commencement of their insulin pump therapy and again at 3 months and then as is clinically indicated.

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Improving diabetic eye disease through insulin pump therapy or islet transplantation

Dr Shareen Forbes, University of Edinburgh

Diabetes is a major cause of blindness. High blood glucose readings are associated with progressive complications from diabetes including those affecting the retina termed diabetic retinopathy. When patients are switched to insulin pump therapy or undergo islet transplantation – a procedure involving the transplantation of donor islets into the liver, which may lead to insulin independence, an improvement in their diabetes control may occur leading to an improvement in diabetic retinopathy in the longer term. However, following commencement of insulin pump therapy those with poor control and pre-existing diabetic retinopathy who experience a marked improvement in their glucose control are susceptible to progression in diabetic retinopathy within the first year of therapy. This has led us to modify our practise in NHS Lothian: people now have retinal eye screening on commencement of their insulin pump therapy and again at 3 months and then as is clinically indicated.

Retinal eye screening allows the physician to intervene with therapy which might save eyesight. Therefore it is important to understand the particular patient groups may be most at risk for eye disease and the best time at which to perform retinal screening. What has not been studied is how islet transplantation affects retinopathy and how hypoglycaemia and the day to day variability in glucose concentrations relate to retinopathy in both groups of subjects. We will follow subjects who have undergone conversion to insulin pump therapy or islet transplantation and serially examine their vision prior to and after this therapeutic intervention and relate changes in retinopathy to changes in their glucose control. We will use novel techniques of examining glucose control including Continuous Glucose Monitoring Systems which record glucose concentrations every three minutes over a six-day period. These tests will allow us to examine whether progression of retinopathy is related more to the improvement of blood glucose control per se or to a reduction in hyperglycaemia or a reduction in blood glucose variability. Diabetes also affects the nerves, resulting in disability. The study will also allow us to make objective assessments of nerve fibres by measuring vibration sensation in the feet and how this perception changes over time and its relationship to blood glucose control. The study will help inform screening strategies for islet transplantation and help refine those for insulin pump subjects, leading to improved medical outcomes.
Blood sugar control in diabetic patient with eye disease before and after islet cell transplant. In perfect control the lines would lie in the green bands on the graphs.

Rate of deterioration of diabetic eye disease in diabetic patients who have received islet transplantation, are using insulin pumps or who are taking intermittent self-administered insulin injections. Patients with islet transplants or insulin pumps have slower rates of deterioration of diabetic eye disease.
For more information on how you can support us please contact:

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