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Results from UCL Institute of Ophthalmology/Moorfields gene therapy trial

Background and Q&A for journalists

Results from the first gene therapy trial of its kind, undertaken by scientists and clinicians at the UCL Institute of Ophthalmology and Moorfields Eye Hospital, have been announced today.

The launch of the trial was reported in the media in May 2007. The scientists and doctors involved have now published the first results from the trial in the New England Journal of Medicine.

Q: What is gene therapy?

A: Genes are coded messages that describe how specific functions in each cell are carried out. If the gene is corrupted, some functions cannot be performed and this can result in genetic diseases.

Gene therapy (sometimes known as 'gene replacement therapy') is a technique for correcting corrupted genes that are responsible for disease development. The technique aims to replace the corrupted gene with a correct version in the cells where it is needed.

The eye has for some time been considered as a good potential target for gene therapy, because is a relatively simple and accessible organ. It can also be accessed by direct injection – overcoming problems relating to gene delivery.

Q: What is Leber's Congenital Amarousis?

A: Leber's congenital amaurosis (LCA) is a type of inherited retinal degeneration, which causes progressive deterioration in vision, due to an abnormality in a gene called RPE65. This defect prevents normal function of the retina, the light-sensitive layer of cells at the back of the eye. This results in severely impaired vision from a very young age, which deteriorates as the patient gets older. There are currently no effective treatments available.

Q: What was the aim of this trial?

A: The aim of this trial was firstly to find out whether gene therapy for retinal disease is safe, and secondly to find out if it can benefit vision in young adults who already have advanced retinal disease.

Q: Is this technique safe?

A: There are a number of possible side effects of the surgery including retinal tears, unplanned retinal detachment and inflammation. Each of the three adults involved in this trial made a full recovery following surgery and none have developed any serious side effects to date.

Q: Can gene therapy benefit vision?

A: For this trial we included only young adults, who had minimal residual retinal function and could not necessarily expect to benefit. However, we found that that gene therapy significantly improved the night-vision in one of the patients, Steven Howarth (18), even though he already had advanced retinal degeneration.

Sensitive tests of vision (micro-perimetry and dark-adapted perimetry) have shown that his retina has become more sensitive in dim-light. Furthermore, we found that his ability to navigate a simulated night-time street scene was dramatically improved. The combination of these highly sophisticated and rigorously performed techniques provides powerful evidence of a significant improvement in vision.

The microperimetry and dark-adapted perimetry tests are objective and accurate techniques but the importance of the improvements in retinal sensitivity are difficult for a non-specialist to understand. However, the visual mobility test demonstrates the impact of these changes on visual ability even to the non-specialist – as demonstrated in the video we have released.

Q: What is happening in the video?

The first sequence shows the patient navigating a dimly-lit, specially constructed simulation of a night-time street scene before the treatment. The second sequence shows him navigating a different formation of the scene six months after the treatment. Before the operation, he completed the task slowly and made several mistakes, but following the surgery he was able to navigate quickly and without mistakes. The patient is wearing an eye tracker so the team can follow his eye movements and is accompanied to ensure his safety.

Q: What difference has the treatment made to this patient's everyday life?

A: Stephen is now able to see more clearly when outside at night. (We have some quotes that media can use from Stephen).

Q: Will the effects last over time?

A: The improvement in Stephen's vision has been maintained to date. Stephen will be followed for many years to determine the long-term effects.

Q: Why did we treat only the eye with the worse function?

A: Although treatment of the worse eye is likely to be less successful, we wish to avoid side effects to the better eye until the risks and benefits of this experimental treatment have been investigated.

Q: Why did only one subject showed improvement?

A: Stephen had better residual vision than either of other subjects. It is therefore likely that his retina was better preserved prior to treatment and this probably explains the improvement that was not observed in the other subjects.

Q: Why is improvement in just one patient important?

A: Proof of principle has been established because we have shown for the first time that vision can be improved by gene therapy. Our findings suggest that gene therapy can work even in advanced retinal degeneration. Younger patients with less retinal

degeneration are likely to respond with better and more consistent improvement.

Q: This is a childhood disease. Why treat young adults?

A: This is a new treatment strategy for human retinal disease. We needed to determine the possible risks and benefits. Although it is very likely that the greatest improvements in visual function will be seen in young children with early disease, it is not appropriate to treat minors until the risks and benefits have been investigated in adults. For this reason the starting point for this trial was the treatment of young adults with advanced disease.

Q: Why do you think that the outcome will be better in children?

A: We know from animal studies that outcomes of gene therapy are dependent upon the age at which the animal is treated and the degree of degeneration: younger animals and those with less degenerate retina respond better.

Q: Will you be treating younger patients?

A: We have already enrolled children on the trial. We will report the outcome in these young patients in due course.

Q: Is this treatment available now?

A: No. It's important to emphasise that the team are still in the early stages and this is an experimental therapy not yet available to patients. The technique will be trialled in more patients with LCA and we hope to begin trials for other genetic retinal diseases. What these results give us is confidence that this technique is safe and can work - and hope to those with LCA and other eye diseases that this method offers a real and tangible hope of an effective treatment in the future

Q: What background work was conducted before the trial?

A: Previous work using animal models demonstrated that this gene therapy technique could improve and preserve vision. During trials, the vision of dogs with the defect was restored to the extent that they were able to walk through a maze without difficulty; something they could not do before the treatment. As this trial was the first to treat an eye disease using administration of gene therapy vectors to human retinas, the team first carried out extensive pre-clinical testing.

Q: How many people could this treatment potentially benefit?

A: Leber's congenital amaurosis (LCA) is a rare disease, affecting approximately 1 in 50,000 people in the UK. There are various forms of LCA and there are approximately 10 new cases a year of the form that is being treated in this trial.

However, the disease is part of a much larger group of inherited retinal diseases which affect 1 in 3,000, so success in this trial has implications beyond one rare disease as the technology could be used to treat other eye diseases.

Q: What happens next?

A: These results are for the first three patients treated by the team, who are young adults. The trial continues and the team have already begun to treat children with less advanced disease. They anticipate an even better outcome in these younger patients, as they will be treating the disease in the early stages of its development.

The trial is currently funded by the Department of Health until January 2009, so the team will be looking at ways of funding its continuation. They will also look to extend the technology to trials in patients with other forms of retinal degeneration and will be seeking new funding to do this as well.