Moorfields plans human trial for gene therapy

Daithí Ó hAnluain in London

MOORFIELDS Eye Hospital and the Institute of Ophthalmology (IOO) will co-manage a bold gene therapy trial in London next year. The trial will help determine the potential of gene therapy's for ocular disorders.

The planned trial will involve patients with one of the variations of Leber's congenital amaurosis (LCA), a retinal disease which causes patients to lose rod-function. The targeted mutation is a rare defect (1/100,000) in the RPE65gene, but the trial could provide an important proof of principle that could open the way for treatment of other inherited retinal dystrophies.

Robin Ali MD, consultant ophthalmologist at Moorfields and head of the division of molecular therapy at the IOO, presented delegates to the Moorfields Bicentenary Scientific Meeting with a summary of tests to date carried out in animal models and outlined the human trial, for which his associate Professor Tony Moore is the lead clinician.

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Robin Ali MD

Gene replacement therapy

As a proof of principle, the team first tested gene replacement therapy in a mouse model of retinal dystrophy due to a defect in gene encoding peripherin-2, a photoreceptor-specific protein required for the generation of outer segments.

Researchers applied a sub-retinal injection of recombinant adeno-associated virus (rAAV-2) vector carrying a peripherin-2 transgene. This resulted in the formation of discs and the generation of new structures that, in many cases, were morphologically similar to outer segments.

The virus demonstrated stable expression and controlled expression, which means the payload of the virus was produced by cells, but the virus did not reproduce.

The researchers used electron microscopy to establish that there was a structural effect and physiological effect, post-injection. The restoration of photoreceptor structural integrity was reflected in significantly improved electroretinography (ERG) responses.

Further experiments tested the feasibility of the same approach for LCA. Mice received a double injection of the rAAV-2 vector carrying RPE65 in the right eye at five weeks old. The left eye was a control. Three weeks post injection the mice showed improved ERG results. Again, the team demonstrated improved visual function. Similar trials were successful in dogs.

This follows from earlier work in the US, where Dr Gregory M Acland and colleagues treated Briard dogs with the RPE65 defect with a gene therapy. Dogs that received the treatment could negotiate a maze, but controls could not (Acland et al Nature Genetics Vol. 28 may 2001).

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Eye is good target for gene therapy

In the past, gene therapies have produced mixed results. In 2002 researchers in France halted a trial treatment for X-SCID, or "bubble boy" disease when one of the patients developed leukaemia. This very low risk was anticipated, but it casts a shadow over gene therapy.

The eye, however, is particularly suited to gene therapy. It is easily accessible and allows localised exposure of the target tissue to therapeutic agents with limited risk from the systemic effect seen in the French trial. The success of RPE65 research in the UK prompted the Department of Health there to provide funding of £1m for a human trial.

""RPE65 defect is the most suitable condition for the first clinical trial of gene therapy for an inherited retinal degeneration," Dr Ali, told delegates at the Moorfields meeting. There are already well-established, non-invasive procedures to assess ocular structure and function, and these are much more advanced than those used on any other organ, he added.

He said LCA is a severe disease, ERG results can provide a rapid assessment of initial efficacy and that RPE defects are generally more amenable to treatment. In addition, it is a rare example of an eye disease linked to a single, missing gene.

Clinical trials planned

Currently work at Moorfields focuses on preparation for the human trial. The virus vector is in preclinical testing in mouse and large animals and a clinical grade vector will be produced. Researchers have already identified patients for the planned trial.

Should this trial prove successful, gene therapy trials for a whole host of ocular diseases are likely to follow.

"The common theme with retinal diseases is proteins. In AMD, proteins are driving angiogenesis. In dominant Retinitis Pigmentosa (RP), the protein is abnormal. And in LCA, the protein is absent. It underlines why this research is important and how it could potentially open the door to new treatments – or at least promising trials to follow," said Lyndon da Cruz FRCOphth PhD, consultant ophthalmologist at Moorfields Eye Hospital and a member of the research team, in an interview with *EuroTimes*.

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Lyndon da Cruz FRCOphth Phd

Currently work is also underway in London to study gene therapy for retinitis pigmentosa (RP), AMD and diabetic retinopathy, as well as a host of other inherited retinal degenerations and posterior uveitis. There is a strong body of work developing on angiogenesis with relevance for several disorders.

Nonetheless, the challenges are great. LCA is an ideal test candidate because it is a single gene pathology, but many conditions like AMD are multi-gene and, indeed, multifactorial.

"I'm losing count with RP, but that has I think now 30 or 40 genes associated with various forms of it, and even within those there are different mutation types, so RP isn't one condition, it's an appearance and a type of degeneration. You'll need a different treatment for each one. We hope to solve that problem, but we want to prove the therapy with one condition in the first instance," said Dr da Cruz said.

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