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Ocular gene therapy trials due to report this year

Keeping an eye on clinical trials in 2008

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This year promises to be an exciting one for ocular gene therapy. Last year saw the start of three clinical trials of gene therapy for inherited retinal degeneration. These trials mark the culmination of decades of international research in ocular genetics and experimental ophthalmology and by the end of 2008 some of the results from the three trials are likely to be available.

The eye has unique advantages as a target organ for the development of novel therapies and is often regarded as a valuable model system for gene therapy. It is a relatively small target organ with highly compartmentalized anatomy in which it is possible to deliver small volumes of adeno-associated virus or lentiviral-based vectors very precisely and obtain efficient and stable transduction of a variety of ocular tissues with attenuated immune responses. The risks of systemic side effects for eye procedures are minimal. Furthermore, if only one eye is treated, the untreated eye may serve as a useful control. Although gene therapy might be used first as a treatment for relatively rare single gene disorders, it also offers a potentially powerful modality for the management of much more common complex acquired disorders, such as those involving angiogenesis.

The potential for gene therapy in this area has benefited from significant progress in the mapping and cloning of retinal disease genes, of which more than 120 have been identified to date. Significant successes have also been achieved by gene replacement strategies in models of inherited retinal degenerations due to loss-of-function mutations in genes encoding proteins that mediate critical functions in photoreceptors and retinal pigment epithelium cells.[1]

Inherited retinal degenerations resulting from single gene defects affect approximately one in every 3000 individuals. As there is no treatment option currently available, this condition provides a unique context in which to definitively determine the value of ocular gene therapy. The three clinical trials are all aimed at the same form of inherited retinal degeneration: early-onset severe retinal degeneration (Leber's congenital amaurosis. This is caused by defects in the gene encoding the enzyme RPE65, which is an isomerase critical for normal retinoid cycling in the retinal pigment epithelium. Individuals with defects in RPE65 have absent/very poor night vision and poor central vision with a predictably progressive degeneration. As they can have relatively well-preserved retinal structure, gene replacement offers the possibility of an improvement in visual function, measurable within the short term. The demonstration of long-term functional improvement following gene replacement of RPE65 in preclinical models has supported the development of the three trials. Several groups have demonstrated that adeno-associated virus-mediated gene replacement therapy in the Swedish Briard dog, which is homozygous for a null mutation in RPE65, can dramatically improve both retinal function and visual behaviour after a single subretinal injection of vector.[2–5]

In February 2007, the first clinical trial began in the United Kingdom at UCL Institute of Ophthalmology and Moorfields Eye Hospital. By the end of the year, two additional trials had started in the United States—one at Scheie's Center for Hereditary Retinal Degenerations, University of Pennsylvania and the University of Florida College of Medicine in Gainesville and the other at the University of Pennsylvania and Children's Hospital of Philadelphia. Each of these trials have started with adult subjects and have a strong emphasis on evaluating safety and toxicity but they will also address the beneficial potential in terms of visual function. Preclinical work suggests that gene replacement therapy for RPE65 is most likely to be effective in affected individuals at an early age as younger subjects have less advanced retinal degeneration. If the feasibility and safety of subretinal vector delivery can be demonstrated in young adults, then children will be included in subsequent phases of each trial.

Is there any value in running three similar trials concurrently? All the clinical trials for RPE65 will use similar adeno-associated virus vectors but the protocols have important differences in terms of vector design and inclusion criteria. adeno-associated viruses have been selected because they target retinal pigment epithelium cells stably and have a strong track record of safety in preclinical work. The vectors differ, however, in their promoter sequences. The use of a powerful constitutive promoter is likely to maximize the efficiency of RPE65 expression. An attempt to achieve targeted physiological expression using the endogenous RPE65 promoter might result in a different therapeutic effect or safety profile. The differences in study protocol between these trials in terms of vector titre, promoter sequences and inclusion criteria are expected to yield complementary data that will help to inform on optimal vector design and define a window of opportunity for the timing of intervention.

The three clinical studies are a landmark for the development of ocular gene therapy. The series of trials in the United Kingdom and the United States will help to determine the safety of subretinal vector delivery and is widely expected to demonstrate the therapeutic potential of gene therapy for inherited retinal diseases. It is hoped that the present trials will pave the way for subsequent studies to determine the value of gene therapy in other forms of Leber's congenital amaurosis, in other inherited retinal degenerations and in complex acquired ocular disorders. The prospect of gene therapy offers hope to many thousands of individuals with inherited blindness, for which no treatment is currently available. The trials are already attracting considerable interest among people with inherited blindness, ophthalmologists and the gene therapy community. Although it is expected that they will demonstrate a clear benefit of applied gene

therapy, the first clinical trials for inherited disease will also have important implications for the field and it is critically important that expectations are not raised disproportionately and the results are interpreted in an appropriately balanced fashion. ■

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