

Reflection on the Efficacy of Gene Therapy in the Treatment of Inherited Retinal Degeneration

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Editorial

Inherited retinal degeneration is a group of genetic retinal disorders characterized by the death of photoreceptor cells. Over 150 genes are associated with inherited retinal degeneration; the proteins encoded by these genes are required not only for photoreceptor development, maintenance, photo transduction and synaptic transmission but also for retinal pigment epithelium cell integrity and function [1]. The use of animal models of inherited retinal degeneration facilitates understanding of the underlying disease mechanisms and allows assessment of preclinical gene-replacement treatments. Gene therapy has been performed in animal models with different types of retinal degeneration (e.g. Leber congenital amaurosis (LCA), retinitis pigmentosa, and cone-rod dystrophies) and has been shown to significantly improve visual function [2]. Clinical characterization and genetic diagnosis of patients with inherited retinal diseases offer opportunities for the evaluation of gene therapy in clinical trials. About 8 years ago, three independent groups carried out clinical gene therapy in young patients who had LCA due to mutations in the RPE65 gene [3-5]. These studies were the first *in vivo* clinical tests to assess both safety and efficacy of gene therapy. Following subretinal injection of adeno-associated virus, no adverse ocular effects or systemic toxicity were observed in any of the treated patients, while the majority of patients were reported to exhibit improvements in aspects of visual function. A follow-up study of one of the patient group found that the improved vision persisted for at least three years, even though the photoreceptor degeneration continued unabated [6]. In fact, the photoreceptor death rate in these patients was similar to that seen in untreated LCA patients with RPE65 mutations. Further long-term follow-up study of this treated group showed that the retinal area of improved visual sensitivity slowly expanded over a period of 1 to 3 years then subsequently diminished [7]. The outer nuclear layer showed progressive thinning throughout the long post-treatment period. Similar continuous photoreceptor cell death was observed in the naturally occurring RPE65 mutant canine model when gene therapy was initiated after the onset of retinal degeneration [6]. However, treatment of these LCA dogs before the onset of retinal degeneration resulted in the arrest of photoreceptor death. Interestingly, gene therapy intervention at initial, mid and late-stage in a different canine retinal atrophy model (XLPR2) were all effective in rescuing vision and arresting photoreceptor loss [8], suggesting that the efficacy of gene therapy may be influenced by the specific genetic defect being targeted. The results from the gene augmentation studies in both humans and dogs suggest that, to be successful, gene therapy must be carried out prior to the onset of degeneration or in combination with neuroprotective agents. Photoreceptor death is a highly complex process; many damaging factors are believed to be involved and different death mechanisms have been hypothesized [1]. A number of agents including antioxidants, trophic factors, and insulin can slow photoreceptor death to a limited extent [1]. However, currently there is no agent effective in completely preventing photoreceptor death in patients with retinal diseases. More research is urgently needed to elucidate the underlying molecular mechanisms of inherited retinal degeneration, which in turn will support the discovery of novel pharmacological agents to slow or prevent photoreceptor death. The findings from LCA gene therapy have implications for the design of gene therapy intervention for other

genetic forms of retinal degeneration. For example, the late-period worsening of visual performance (following the initial post-treatment improvement) that has been observed in treated LCA patients is possibly due to a decline in the expression of the RPE65 transgene and consequent deficiency in the visual cycle [7]. If this is the case, an appropriate promoter will be needed to drive the targeted transgene in photoreceptors at a natural level in the long term. Indeed, our lab is developing such an approach by using a human RPGR promoter to control human RPGR expression in patients with X-linked retinitis pigmentosa [9].

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