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Gene Therapy for Retinal Diseases Is Within Sight

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Advances in Vitreoretinal Disease Management

Many vitreoretinal pathologies have witnessed impressive advances in their management over the past decade. Most of these advances have involved pharmacologic innovation aimed at controlling exudative diseases of the retina, including neovascular age-related macular degeneration (AMD),[1-3] macular edema secondary to diabetic retinopathy,[4] and venous occlusive diseases.[5-7] These advances have relied upon a relatively simple treatment strategy: intraocular delivery of a pharmacologic agent by direct intravitreal injection with a needle advanced through the pars plana.

Other, more complex treatment approaches to vitreoretinal disorders have made substantial advances over the same period but have yet to make significant clinical impact. For example, remarkable progress has been achieved in both the use of retinal prosthetic systems[8] and stem cell delivery to treat retinal degeneration.[9] Finally, gene therapy is possibly the most targeted and exciting of these recent advances whose promise is just beginning to be manifest in the management of inherited retinal diseases.

Inherited Retinopathies

Inherited retinopathies are common blinding disorders that affect about 1 in 2000 people worldwide.[10] Most of these disorders currently have no available treatment options. Although the inherited retinopathies are phenotypically and genetically heterogeneous, with more than 150 causative mutations identified to date, most are monogenic, with a single genetic defect accounting for visual dysfunction. The causative genes are most commonly expressed in the photoreceptors and to a lesser extent in the retinal pigment epithelium (RPE).[11] Some of the most frequent and severe forms of inherited retinopathies include Leber congenital amaurosis, retinitis pigmentosa, Stargardt disease, and choroideremia.[11]

Why Target Retinal Disease With Gene Therapy?

Related to retinal disease management, "gene therapy" refers to the incorporation of new DNA into cells, either to supply a gene that is missing or not functioning in that cell or to supply a therapeutic gene. Several characteristics make the retina an ideal target for gene therapy:

• The intraocular environment is easily accessed through the pars plana by a relatively noninvasive approach compared with other internal organs, and the amount of retinal tissue is relatively small compared with most visceral organ systems.

• The blood-retinal barrier creates an intraocular environment that is relatively isolated from the systemic immune system, affording some degree of tolerance for administered foreign antigens and minimization of systemic vector spread.

• Treatment outcomes can be easily monitored both subjectively (eg, with patient visual acuity) and objectively (eg, with electrophysiology and optical coherence tomography).

• The ordered, epithelial architecture of retinal layers allows an administered vector easy access to entire cell populations.

The 3 most commonly used vector systems for retinal gene delivery are adenoviral vectors, lentiviral vectors, and recombinant adeno-associated virus (rAAV) vectors. The most widely used vectors for ocular gene therapy -- rAAV

vectors -- do not contain viral genes but rather are engineered to contain specific DNA sequences that can be used for therapeutic purposes. rAAV is able to transduce both dividing and nondividing cells, and different serotypes can be used to preferentially target specific retinal cell types, including the photoreceptors, RPE, or ganglion cells.[12]

The combination of an accessible target tissue (the retina) with multiple monogenic blinding diseases with no available treatment spurred extensive research over the past 20 years. Building on successful animal models, we are currently witnessing the translation of this basic science research to human clinical application.

Retinal Gene Therapy to Replace a Defective Gene Product: Early Results of Human Clinical Trials

Leber Congenital Amaurosis Type 2 (Caused by *RPE65* Mutations)

Leber congenital amaurosis (LCA) is a severe, blinding, typically autosomal recessive retinopathy resulting from mutation in one of more than a dozen causative genes.[13] Affected people are usually diagnosed within the first few months of life, typically being born with very poor visual function and experiencing progressive visual decline that often leads to total blindness. Mutations in the *RPE65* gene disrupt the visual-retinoid cycle and impair production of the visual pigments rhodopsin and cone opsin with concomitant toxic accumulation of all-trans-retinyl esters, promoting photoreceptor death and leading to LCA type 2 (LCA2).

Despite its rarity, affecting < 1 in 1 million live births, LCA2 is an ideal pathology for the application of retinal gene therapy because, although photoreceptors degenerate, RPE cells are relatively well preserved; therefore, restoration of *RPE65* function in RPE cells was hypothesized to lead to photoreceptor reactivation and restoration of sight.[11]

On the basis of this reasoning, a tremendous amount of research has focused on the development of a gene-based therapy for LCA2, and it has been exceptionally successful in a multitude of animal models. In canine, porcine, and rodent LCA2 models, rAAV vectors have been used to deliver functional retinoid isomerohydrolase, restoring retinal function with dramatic visual improvement.[14]

Building on this success, phase 1 human clinical trials have been performed. For example, 3-year data were reported from a dose-escalation, phase 1 study of 15 patients aged 11-30 years who were treated with subretinal injection of a rAAV vector expressing *RPE65*. It revealed no systemic toxicity, good ocular tolerance, and improvement in visual function in all patients -- dramatically in some.[15] A 24-patient phase 3 trial is currently recruiting patients in Iowa and Pennsylvania.[16]

Choroideremia

Choroideremia is an X-linked recessive retinal degenerative disease affecting about 1 in 50,000 people with loss of night vision beginning in the first decade of life, followed by gradual peripheral visual loss with progression to blindness by the fifth decade in most patients. Retinal degeneration is caused by prenylation deficiency due to absence of Rab escort protein-1 (REP-1) encoded by the *CHM* gene.

Partial results of a phase 1 study involving 6 men aged 35-63 years who were treated with subretinal injections of a rAAV vector expressing REP-1 were recently published.[17,18] Mean visual acuity improved by 3.8 letters among all patients, with 2 patients experiencing substantial improvements in visual acuity of 21 and 11 letters (over 4 and 2 lines of visual acuity, respectively).

Retinal Gene Therapy to Supply a Therapeutic Gene

Neovascular Retinal Diseases

In addition to replacing dysfunctional gene products caused by mutations in a person's germline, gene therapy can serve as a platform for drug delivery. For example, any retinal disease that could benefit from local production of a

specific RNA or protein is a potential candidate for gene therapy.

Currently, therapies applied for neovascular AMD involve pharmacologic agents that block vascular endothelial growth factor (VEGF). These medications achieve VEGF suppression remarkably well, but the relatively short half-lives of these biological proteins, on the order of hours to days, often necessitate monthly administration for maximal clinical effect and visual benefit, especially in recalcitrant cases.[19,20] Repeated treatments incur additional patient risks and inconvenience.

The need for longer-acting therapeutics may be fulfilled with gene therapy. For example, an adenoviral vector expressing pigment epithelium-derived factor that inhibits angiogenesis was used with success in a phase 1 trial.[21] Currently, a phase 1 trial is under way to evaluate an intravitreally administered rAAV vector expressing a soluble portion of a VEGF receptor intended to block VEGF (sFlt01).[22]

Expanding Gene Therapy Targets

Early results of gene therapy studies for inherited retinopathies are compelling; phase 1 human clinical trials have demonstrated safe and successful targeting of mutant genes involving the RPE (LCA2) and photoreceptors (choroideremia). If ongoing trials, including a phase 3 trial for LCA2 treatment, are successful, additional monogenic retinopathies will certainly be targeted as treatment horizons expand. Early results from local intraocular expression of specific therapeutic proteins through gene therapy are also promising.

Ideally, retinal gene therapy targets will be expanded to include multigenic diseases, such as dry AMD. Dry AMD has a substantial genetic component but many involved loci,[23] and the only current treatment options involve lifestyle modifications, such as smoking cessation,[24] cardiovascular risk factor optimization, and AREDS2 (Age-Related Eye Disease Study 2) vitamin supplementation[25] aimed at slowing disease progression.

The future is certainly bright when considering gene therapy for retinal diseases. Unfortunately, only the tip of the therapeutic iceberg is still visible today, with many challenges remaining. With continued development and refinement of these technologies and techniques, the clinical application of gene therapy vectors to treat a host of retinal diseases in the operating room, and even in the clinic, appears to be within sight.

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