First step made in glaucoma gene therapy

MAYO Clinic researchers have demonstrated they can permanently transfer a functioning gene to targeted tissues within the eye. This success in animals is a first step in using gene therapy to treat glaucoma.

Researchers transferred a phosphorescent green protein naturally found in a species of jellyfish. A single injection through the surface of the cornea introduced the jellyfish gene. The protein was encased in a specialised viral vector delivery system.

The authors wanted to address a problem impeding research into genetic mutations associated with glaucoma and glaucoma gene therapy. They sought to achieve permanent, targeted transgene expression in the trabecular meshwork.

"Lentiviral vectors are known to transduce human donor eye trabecular meshwork ex vivo, but efficacy in vivo has not been shown," the authors wrote.

More generally in the field of gene therapy, the authors believed that distinctive properties of the intraocular aqueous circulation could facilitate solving problems of accessibility, targeting, and scale that have hindered realisation of gene therapy in other settings.

The authors developed a domestic cat model to perform long-term in vivo studies. Following dose-response studies in primary human trabecular meshwork cells, 19 cats received anterior chamber injections of stepped doses (106—108 transduction units) of lentiviral vectors encoding different marker transgenes (β-galactosidase, Aequorea victoria green fluorescent protein [GFP], or Renilla reniformis GFP). Animals were monitored serially for transgene expression and IOP.

The experiment achieved high-grade, stable transgene expression in the trabecular meshwork. It was monitored non-invasively over time in living animals. Extensive expression resulted after a single transcorneal injection, persisted for at least 10 months (time of death in the present studies), and was targeted to the trabecular meshwork. The initial IOP did not differ significantly from the IOP at the end of the study. Aequorea GFP was superior to Renilla GFP. The viral vectors were effective enough to cause GFP-specific over-expression cytotoxicity at the highest dose, which was solved by dose reduction.

The authors concluded that high-grade transgene expression in this large-animal model persisted stably for at least 10 months after a single transcorneal lentiviral vector injection. It was highly targeted and could be monitored serially and non-invasively in living animals. They noted that these studies provide a basis for developing realistic disease models and administering glaucoma gene therapy.

When the vector reached the intended destination in eyes of laboratory cats, the vector’s cargo gene produced the phosphorescent jellyfish protein in the cats’ eyes. Researchers knew they were successful because the cats’ eyes turned green when viewed with ultraviolet light at the targeted area. They also knew the effect was permanent because the cats’ eyes continue to glow green more than a year after the procedure. The green-eyed cats have normal vision and were none the worse for the gene transfer.

"The main message here is that lentiviral vectors have promise for treating diseases such as diabetic retinopathy and AMD. "The general approach of using lentiviral vectors has promise for treating eye diseases that are chronic, if a suitable therapeutic gene for the given disease is used."