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GENE THERAPY RESCUES PHOTORECEPTOR FUNCTION, MORPHOLOGY AND SURVIVAL IN A PRE-CLINICAL MODEL OF CDHR1-ASSOCIATED RETINAL DEGENERATION

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Purpose:

To evaluate the long-term efficacy and safety of retinal gene therapy in a pre-clinical model of CDHR1-associated retinal degeneration – an as yet untreatable, blinding disorder characterised by progressive cone and rod photoreceptor degeneration that may affect over 200,000 individuals worldwide.

Methods:

Cdhr1-/- (n=28) and C57BL/6J control mice (n=23) underwent paired superior sub-retinal injections of AAV8.GRK1.CDHR1 (1.5x10E8 vector genomes) and PBS vehicle control in the fellow eye at 3-4 weeks of age. Dark- and light-adapted electroretinography (ERG) responses (to 12-months post-injection), photoreceptor layer thickness measurements on optical coherence tomography (OCT) imaging (to 18-months post-injection) and scotopic (0.01 lux) and photopic (1000 lux) optomotor behavioural responses (to 22-months post-injection) were compared between AAV- and PBS-injected control eyes. Outer retinal ultrastructure was evaluated by electron microscopy at 22-months post-injection.

Results:

In Cdhr1-/- mice, AAV8.GRK1.CDHR1 rescued A-wave amplitudes ($p<0.0001$) and B-wave amplitudes ($p<0.0001$) on dark-adapted ERG and B-wave response amplitudes on light-adapted ERG ($p<0.0001$) compared to PBS-injected eyes, sustained to 12-months post-injection. Scotopic and photopic optomotor behavioural responses were preserved in AAV-injected Cdhr1-/- eyes only ($p<0.0001$), to 21-months post-injection. OCT imaging demonstrated preservation of the photoreceptor layer ($p<0.0001$) and photoreceptor outer segment regeneration ($p<0.0001$) in AAV-injected Cdhr1-/- eyes only. Full-length outer segment regeneration was confirmed on electron microscopy. In C57BL/6J mice, ERG responses, photoreceptor thickness measurements and optomotor responses were similar in treated versus control eyes ($p>0.05$ for all comparisons).

Conclusions:

These data provide proof-of-principle of the efficacy and safety of CDHR1 gene therapy in a pre-clinical model of CDHR1-associated retinal degeneration. Rod and cone rescue occur through prevention of photoreceptor cell death and photoreceptor outer segment regeneration. A follow-on clinical trial is warranted.