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"Exploring Genetic Therapeutic Strategies to Combat Vision Loss in Usher Syndrome Type 1C"

Background: Usher Syndrome (USH) is an autosomal recessive genetic disorder that is the most common cause of hereditary deaf-blindness in the world. Of the four clinical types of Usher Syndrome (USH1-4), USH1 is the most severe, characterized by congenital sensorineural hearing loss and vestibular areflexia, and adolescent onset of retinitis pigmentosa. Nearly all USH1 cases in the Acadian populations of Louisiana are cause by the *USH1C* c.216G>A mutation (216A), which causes aberrant RNA splicing resulting in a truncated harmonin protein. Harmonin is a structural protein that is expressed in cochlear hair cells and photoreceptors. Here we explore various genetic therapeutic strategies to address the lack of full-length harmonin in a mouse model of Usher Syndrome Type1C (USH1C). Previously, we showed modest improvements to vision in USH1C mice using gene replacement and antisense therapies. In this study, we optimize gene replacement delivery and antisense oligonucleotide chemistry to improve upon these results.

Methods: Wild-type and USH1C^{216AA} mice received a single dose of either a reporter AAV (AAV44.9-(E531D)-CBA-GFP) vector or antisense oligonucleotides with a 2'OMe backbone chemistry (ASO) via intravitreal injection (IVI). To ~~assess~~assess AAV transduction, GFP expression was measured using fluorescent fundoscopy and immunohistochemistry. To assess splicing correction with ASOs, RT-PCR and Next Generation Sequencing (NGS) was used on isolated retinal RNA.

Results: Preliminary results show AAV-mediated GFP expression with fundus imaging and immunohistochemistry. Retinal cell-type specific markers are pending to confirm tropism in the retina. Sequencing analyses of ASO treated mice is pending.

Conclusion: These data suggests that the AAV44.9 vector can transduce cells in the mouse retina via an intravitreal injection delivery route. Future studies will test the therapeutic effect of AAV-Ush1c versus ASO treatment on visual function in USH1C mice.