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"Tropism of novel AAV capsid variants in the inner ear"

Background: Usher syndrome (Usher) is the leading genetic cause of combined deaf-blindness. Of the three clinical types, type 1 (USH1) is the most severe with congenital sensorineural hearing impairment and vestibular dysfunction, and adolescent onset of retinitis pigmentosa. While the genetics of Usher is well understood, the treatment options for these patients are limited. To fill this gap, we created a mouse model of Type 1C Usher (USH1C*)* that contains the splice site mutation (*USH1C* c.216G>A) responsible for USH1C in patients. USH1C mice have hearing, balance, and visual dysfunction similar to patients. Additionally, the expression of harmonin protein, encoded by the *USH1C* gene, is significantly reduced in hair cells in the inner ear and photoreceptors in the retinas of USH1C mice. Our long-term goals are to develop an AAV-based gene replacement therapy for the deafness, imbalance, and vision loss in USH1C. The objective of this study is to determine the cell specificity of newly engineered AAV capsids in the inner ear.

Methods: Wild-type (WT) mice were treated with 1.9x10E12 gc/ml of AAV2.P2-V1(Y-F+T-V)-CBA-GFP, AAV2.P2-V3-CBA-GFP, or saline at postnatal (P) day 1-2 by semicircular canal (SCC) injection. For a preliminary assessment of treatment safety, hearing was measured by auditory brainstem response (ABR) analysis at 1 month-of-age. Temporal bones were then harvested, and the cochlear and vestibular end organs were micro-dissected to assess viral transduction using immunohistochemistry analysis.

Results: Preliminary results of mice treated with AAV2.P2-V1(Y-F+T-V)-CBA-GFP virus show GFP signal in cochlear and vestibular hair cell supporting cells. GFP signal was not detected in cochlear or vestibular cells in mice treated with AAV2.P2-V3-CBA-GFP virus. Mice treated by SCC injection with AAVs or saline had ABR thresholds similar to untreated WT control mice.

Conclusion: Our results show that injection of novel AAV vectors via the SCC leads to safe and effective transduction of cochlear and vestibular cells in mice. Studies are ongoing to evaluate additional novel capsids to further expand the toolbox for effectively treating diseases of the inner ear.