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"Effect of Antisense Oligonucleotide (ASO29) Treatment on Usher 1C Type Mice Hearing and Vestibular Function"

Background: Usher Syndrome is the most common form of congenital combined deafness and blindness. At least one variant, Usher 1C, has high prevalence among the Acadian population in Southeast Louisiana. This type presents with additional vestibular deficits, including balance dysfunction. Previous work using the USH1C knock-in mouse model from the Lentz laboratory at LSUHSC-NO showed that antisense oligonucleotide (ASO) therapy can rescue sensory function. Our long-term goal is to optimize the ASO therapy to maximize tolerance and therapeutic effects. Toward that end, this project focuses on testing the effect of a specific dosage (300 µg I.P. injection) of ASO29 on hearing and vestibular function. The central hypothesis is that this dose (I.P. injections) will significantly recover hearing and balance function in treated USH1C mutant mice compared to untreated mutants.

Methods: Four tests evaluated hearing and vestibular function in 1 y.o. male and female B6-129S6 strain mice from the three experimental groups (mutant, wildtype (WT), ASO treated mutant). Hearing thresholds were determined using Auditory Brainstem Responses (ABR). Vestibular function was determined using three different behavior tests: open field circling, rotarod, and balance beam. USH1C mice have elevated tone thresholds in ABR tests and exhibit severely inhibited vestibular function, causing mice to repetitively exhibit circling behavior. Thus, circling automated behavior tests measured the number of rotations per 120 s. In contrast, rotarod behavioral tests evaluate the duration of time subjects can remain on a spinning rod. Finally, the balance beam behavior test measures the time needed to cross the suspended beam without falling (i.e., less time indicates better balance and coordination).

Results: Distance Travelled in Circling Test: statistically significant difference between the Usher and ASO29 mice groups. There is no significant difference between the WT group and the ASO29 group. Circling behavior: on average, ASO29 group made less rotations/120 sec than even in the WT group and there is a significant difference between the ASO29 group and the Usher group. The reduced number of rotations for the ASO29 group shows an improvement in vestibular function. Balance Beam: the untreated USH group did not complete enough trials without falling to measure an average. The ASO29 and WT groups are not significantly different ($P > 0.05$). When looking at the percentage of trials completed, only the USH group completed less than 100%, suggesting ASO29 drug can help to recover vestibular function of the mutant mice. Rotarod Data: ASO29 group is significantly different compared to the USH group but not different compared to the WT group. The ASO29 group had greater latency to fall (s) which shows a recovery of vestibular function. Auditory Brainstem Response: In two-way ANOVA, there were significant main effects of mouse type ($P<0.001$) and stimulus frequency ($P=0.0006$) on thresholds. In post-hoc analysis of mouse type, ASO29 treated mutant mice thresholds were significantly lower than untreated mutants ($P<.001$) suggestion some, although incomplete, rescue.

The rationale for this research is that once the treatment is optimized, we will understand how best to administer the ASO drug in clinical populations affected by this disease.