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"Optimizing antisense oligonucleotide chemistry for the treatment of hearing loss and imbalance in Usher Syndrome"

Introduction: Usher syndrome (Usher) is a rare genetic disorder characterized by the loss of hearing, vestibular, and visual function. There are 3 main clinical typers (Usher 1, 2, 3) classified by severity and onset of hearing and vision loss. Usher type 1C (USH1C) is a severe form, caused by mutations in the *USH1C* gene which encodes harmonin, a structural protein critical to the function of hair cells and photoreceptors. USH1C is the most common Usher 1 type in the Acadian populations of Louisiana and Canada due to founder mutation in the *USH1C* gene (c.216G>A(216A)). The 216A mutation causes aberrant splicing that leads to a truncated harmonin protein. USH1C patients have profound congenital hearing loss and balance dysfunction, and progressive vision loss due to retinitis pigmentosa in early childhood. Our long-term goals are to restore a functional, full length harmonin protein at an early disease stage to minimize disease morbidity and prevent or delay progression. We have previously shown that a novel antisense oligonucleotide (ASO-29) therapy targeting this mutation transiently restores hearing, balance, and vision in an USH1C murine model. To further develop this drug, various ASO chemistries targeting the 216A mutation were tested for efficacy in improving hearing and balance in USH1C mice.

Methods: USH1C mice were treated via intraperitoneal injection at postnatal day 2 with 300 µg of 216A-targeting ASOs on a 2' methoxyethyl (ASO-29) or morpholino (MO-29) backbone chemistry, or a combination of the two chemistries (COMBO). Hearing function and balance behavior were assessed in 1- and 3-month-old USH1C -treated, -untreated, and wildtype (WT) littermates using auditory-evoked brainstem response (ABR), and rotarod and balance beam analyses, respectively.

Results: USH1C mice treated with ASO-29, MO-29, or COMBO therapy showed moderate rescue of ABR thresholds at 1- and 3-months of age compared with untreated USH1C mice. Additionally, USH1C mice treated with ASO-29, MO-29, or COMBO therapy showed improved latency-to-fall on the rotarod and time-to-traverse on the balance beam compared with untreated USH1C littermates. Latency-to-fall on the rotarod was not statistically different from WT mice at either age following treatment with ASO-29 or MO-29 whereas mice treated with the COMBO were statistically different from the WT mice.

Conclusions: These preliminary data show that ASO-29, MO-29, and COMBO therapy provide therapeutic benefits to hearing and balance behavior in USH1C mice and supports the potential of antisense treatment to restore hearing and vestibular function in Usher syndrome.