11 Combined transgene and intron-derived miRNA therapy for the treatment of SCA1

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Spinocerebellar ataxia type I (SCA1) is an autosomal dominant neurodegenerative disease caused by a polygluatmine expansion within ataxin 1 (ATXN1) protein. We have previously demonstrated that virally expressed RNA interference (RNAi) molecules targeting ATXN1 can both prevent and reverse disease phenotypes in a mouse model of SCA1. Additionally, we have shown that overexpression of the highly conserved ATXN1 paralog, ataxin 1-like (ATXN1L) can improve disease readouts when delivered to SCA1 mice pre-symptomatically.

Here we combined these approaches in a single transgene, with the goal of reducing the viral dose for effective therapy. Dual expression was achieved by incorporating a miRNA targeting human ATXN1 (miS1) into an upstream intron of a human ATXN1L (hATXN1L) minigene (AAV.hATXN1L int2 miS1). In proof-of-concept experiments, vectors were injected directly into the cerebellum of pre-symptomatic SCA1 mice at varying doses. Tissues were harvested three weeks post-injection and analyzed for transgene expression and RNA processing.

Tissue analysis revealed that our dual expression transgene is effectively processed into mature hATXN1L transcripts and functional miS1 guides. Surprisingly, these vectors achieve greater knockdown and higher transgene expression than our previous separate constructs when delivered at similar doses. This study shows that our novel transgene can be used to test the effects of combined therapy for SCA1, and may significantly reduce the viral load required for therapeutic benefit. Ongoing, long-term studies will assess the ability of these constructs to reverse disease phenotypes in SCA1 mice.