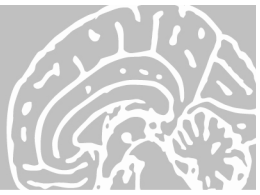
Gene Silencing Therapy in ALS, Spinal Muscular Atrophy, Huntington's Disease and Beyond



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The genes whose expression causes human neurodegenerative disease are widely expressed, producing damage not only within the most vulnerable neurons but also within their partner neurons and glia. This is certainly true for Amyotrophic Lateral Sclerosis (ALS), some instances of which are caused by mutation in the ubiquitously expressed superoxide dismutase (SOD1). Despite absence of consensus on the mechanism(s) of toxicity, slowed disease progression has been achieved by a clinically feasible infusion into the nervous system of antisense oligonucleotides (ASOs) that direct RNase H-dependent destruction of SOD1 mRNA within the nervous system. A trial initiated in 2010 demonstrated the safety of an SOD1 targeting ASO and a follow up trial with an improved ASO with is anticipated to initiate in fall, 2015.

Huntington's disease is caused by toxicity from CAG-repeat expansions in the widely expressed Huntington gene. In multiple rodent examples, ASO infusion to catalyze rapid degradation of huntingtin mRNA mediates partial, sustained reversal of disease that persists much longer than the mRNA knockdown. These findings establish transient ASO-mediated silencing as a feasible therapy for Huntington's disease. A clinical trial with this approach was initiated in July 2015.

The most frequent genetic cause of ALS and the second most common dementia (frontal temporal dementia - FTD) is hexanucleotide expansion in a non-coding region of the C9orf72 gene. Sense and antisense strand repeat-containing RNAs have been found to accumulate in nuclear RNA foci, the hallmark feature of repeat expansion RNA-mediated toxicity. ASOs have been developed that selectively target sense strand repeat-containing RNAs and reduce sense-oriented foci and AUG-independent translation of dipeptide repeat polypeptides encoded by the repeat containing RNA, without affecting overall C9orf72 expression. These findings establish ASO-mediated degradation of repeat-containing RNAs as an attractive therapeutic approach in C9orf72-mediated ALS/FTD.

Overall, ASO infusion into the nervous system to target degradation or alter splicing of pre-mRNAs is widely applicable for therapy in neurodegenerative diseases, with trials ongoing to correct splicing of the SMN2 pre-mRNA in spinal muscular atrophy or reduce mutant huntingtin RNA in Huntington's disease. Other trials are expected to initiate in 2015 or 2016, respectively, for SOD1 and C9orf72-mediated ALS/FTD. Future applications may include targeting α-synuclein, APP, presenilin or tau RNAs to reduce their expression or altering splicing of tau pre-mRNA as therapies for Parkinson's disease, Alzheimer's disease, or chronic brain injury.