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Zoom Registration

Splice-switching Antisense Oligonucleotides for the Treatment of Disease

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Abstract

Antisense oligonucleotides (ASOs) have proven to be an effective therapeutic platform for the treatment of disease. These short, single-stranded, modified nucleotides function by base-pairing with the complementary sequence of an RNA and modulating gene expression in a manner that is dependent on the ASO design and targeting site. We have used ASOs to normalize aberrant gene expression associated with a number of diseases of the nervous system including Alzheimer's and Parkinson's disease and Usher syndrome. One of our approaches is under development for the treatment of CLN3 Batten disease, a fatal, pediatric lysosomal storage disease caused by mutations in a gene encoding the lysosomal membrane protein CLN3. The most common mutation associated with CLN3 Batten is a deletion of exons 7 and 8 (CLN3Δex78), which disrupts the mRNA open reading frame by creating a premature termination codon that results in the production of a truncated protein. We devised a therapeutic strategy for treating CLN3 Batten Disease using an ASO that basepairs to CLN3 pre-mRNA and alters splicing to correct the open reading frame of the mutated transcript. Treatment of CLN3Δex78 neonatal mice by intracerebroventricular injection of the ASO resulted in the desired splicing effect throughout the central nervous system, improved motor deficits associated with the disease in mice, reduced histopathological features of the disease in the brain and extended life in a severe mouse model of the disease. Our results demonstrate that ASO-mediated reading frame correction is a promising therapeutic approach for CLN3 Batten disease.

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