Therapeutic development of a novel siRNA compound targeting alpha-synuclein

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The histopathological hallmarks of Parkinson's disease (PD) include dopamine cell loss in the midbrain substantia nigra pars compacta and the formation of alpha-synuclein-rich intraneuronal inclusions, called Lewy bodies, in surviving neurons. Prior studies support a role for alpha- synuclein in the pathogenesis of PD. These observations have led researchers to hypothesize that suppressing alpha-synuclein production in nigral neurons using a technique known as gene silencing could produce a therapeutic benefit. However, whether this approach could be utilized safely in the adult brain is still unclear since conflicting findings have been reported in the scientific literature.

In this study, we evaluated a novel small interfering RNA (siRNA) compound designed to cause degradation of alpha-synuclein messenger RNA (mRNA), so it cannot be translated into protein. Eighteen adult rhesus macaques were treated with varying concentrations (n= 6 per group) of the siRNA compound which was administered directly into the substantia nigra using a programmable pump and intracranial catheter system. Tolerability of the siRNA treatment was assessed by 1) clinical observations, 2) neurochemical evaluations of striatal tissues for the neurotransmitter dopamine using HPLC-EC methods and 3) histopathological examinations of preserved tissues from the striatum and midbrain regions by a board-certified veterinary pathologist. Histopathological evaluations indicated that the catheter tip was placed in or near the subtantia nigra pars compacta region in all animals. Molecular analyses of mRNA levels from midbrain tissue punches indicated significant silencing of alpha-synuclein expression ranging from 88.3±3.2% at a concentration of 6 mg/mL to 96.6±0.9% at a concentration of 18 mg/mL versus controls. Moreover, alpha-synuclein mRNA suppression was achieved without producing clinically observable symptoms, neurochemical findings or marked neuropathology over a 30-day period of constant siRNA infusion.

Overall, our data support the further evaluation of targeted, intranigral delivery of siRNAs designed to suppress alpha-synuclein mRNA levels as a potential strategy for treating PD. Future directions include evaluating the consequences of suppressing alpha-synuclein production over an even longer period of time.

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