Evaluation of an active immunization therapy targeting synucleinopathy in the seed-induced M83 mouse model.

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Pathological inclusions principally comprised of α-synuclein (αsyn) protein occur in several neurodegenerative diseases which are collectively termed synucleinopathies. The most common synucleinopathies are Parkinson's disease and Lewy body dementia, in which αsyn accumulates in neurons in the form of Lewy bodies. These Lewy bodies are associated with progressive loss of dopaminergic neurons and the hallmark motor symptoms of Parkinsonism. Current Parkinson's treatments are limited, but dozens of potentially therapeutic agents are currently undergoing clinical trial. One such drug is UB-312, a vaccine targeting pathological αsyn protein. Promising phase I clinical trial results were recently reported in which UB-312 demonstrated good tolerability and immunogenicity twenty-nine weeks after initiation of intramuscular (IM) treatment in a Parkinson's patient population. Here, we have performed novel *in vivo* experimentation in the M83 mouse model of synucleinopathy to further mechanistically evaluate UB-312. The M83 mouse overexpresses A53T human αsyn in the brain and spinal cord, but hemizygous animals do not develop any pathology before 18 months of age. Hind-limb IM inoculation of M83 heterozygotes with fibrillar human αsyn seeds induces more aggressive and predictable synucleinopathy resulting in terminal paralysis around 110 days post-administration. In this paradigm, two-month-old, hemizygous M83 mice were inoculated with fibrillar human αsyn and subsequently treated with IM administration of UB-312, adjuvant, or saline at 0,3,6,12, and 15 weeks post-inoculation. UB-312 significantly improved survivability in these inoculated M83 mice relative to saline-treated animals. ELISA-based assessment of serum immunogenicity as well as histological assessments of central nervous system pathology are ongoing.

Sponsored By: Funding provided by the State of Florida

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