**Introduction**

Alpha synuclein (aSyn) plays an important role in Parkinson's disease (PD) with pathological changes of the protein observed in PD patients and mutations/multiplications in the gene leading to PD. Commonly used rodent models overexpress wildtype and mutant forms of aSyn and have been helpful in understanding molecular mechanisms and the role of aSyn in PD pathogenesis. However, the lack of comparable phenotypes makes it challenging to reproduce PD in animal models. Therefore, it is important to have preclinical tools that best suit the scientific questions we want to answer to further our understanding of aSyn biology to develop and evaluate potential therapies for targeting aSyn aggregation. The Michael J. Fox Foundation for Parkinson's Research’s (MJFF) sponsors the development of resources for PD research and drug development communities that endeavors to provide researchers with easy access to rigorously validated preclinical tools for their studies. Here, we present novel viral vectors from the MJFF preclinical tools portfolio that utilize human aSyn to serve as a platform for PD model development.

**1. Validation and Characterization of Human AAV-aSyn as a Model of Nigrostriatal Degeneration**

Plasmid maps for AAV5 Human Alpha Synuclein (A53T) Empty Control (HC), and BFP (HC). CTS is a human hairpin RNA structure placed into the null vector to ensure that WPRE is not translated into protein when there is no open reading frame (ORF) after the WPRE enhancer. Vector optimization for wild type Synuclein was used with 3 µL doses confirmed by aSyn and qPCR. Rats were sacrificed 6 weeks post-injection. Representative images of TH (TH) and aSyn (NF) stained sections were taken. aSyn images were compared to aSyn-CRE expressed at 2:4:12.

**2. Functional Validation of AAV1/2 Human AS3T aSyn and AAV1/2 Empty Vectors**

Plasmid maps for AAV1/2 AS3T aSyn (PA) and AAV1/2 Empty Vector Control (BC). CMV/CBA promoters consisting of chicken beta-actin promoter and herpes simplex virus (HSV) enhancer were used in mouse tissue to ensure high transcription following transduction. The chicken beta-actin promoter for wild type Synuclein spike at 3:4 weeks post-injection.

**3. SNCA miR Viral Vectors Designed to Reduce Human/Mouse aSyn Expression**

Plasmid maps for AAV1/2 hu-syn miR to Human aSyn: AAV1/2-CAG-miR-GFP. Genomic titers were determined by real-time PCR using genomic DNA extracted from virus stocks. The number of VGTS (viral genomes per tissue equivalent) was calculated from the viral load and titer. The transduction efficiency was determined from GFP expression in the striatum of wild-type and aSyn overexpressing mice. The transduction efficiency was determined by counting the number of GFP-positive cells in the striatum of wild-type and aSyn overexpressing mice.

**Summary and More Information**

MJFF is invested in providing the PD research community with high-quality tools and models to support rapid new discoveries and encourage reliable, reproducible data. The tools described in this poster are the result of recent collaborative efforts aimed at generating research-enabling molecular tools to advance Parkinson’s disease research.

Information on other tools for PD-related targets can be found in the Research Tools Catalog at www.michaeljfox.org/toolscatalog. Questions regarding MJFF preclinical tools can be sent to tools@michaeljfox.org.