INFORMATION ON THE ALPHA SYNUCLEIN PRE-FORMED FIBRIL (PFF) ANIMAL MODEL

A significant roadblock to the development of disease-modifying therapeutics for PD has been a lack of reliable, predictive mammalian models that express the neuropathological hallmarks of PD. Recently characterized alpha synuclein-based animal models appear to exhibit many clinically-relevant hallmarks; however, these models have issues pertaining to reproducibility and lack of understanding of the biological properties of alpha synuclein-induced pathology. The replication of these animal models and development of consistent standard operating protocols and outcome measures will enable faster testing of disease-modifying therapeutics. The Michael J. Fox Foundation for Parkinson's Research (MJFF) has funded characterization of preclinical pre-formed fibril rodent models in an effort to validate this model and elucidate mechanisms of alpha synuclein-induced pathology.

HUMAN ALPHA SYNUCLEIN PFFS

Human alpha synuclein monomers available from Proteos are used to generate pre-formed fibrils (PFFs). These monomers can be found in our Tools Catalog under the Protein Category.

Experimental Design			Pathological Measures Investigated					
Species	Injection Site	Timepoints	aSyn Pathology	Nigrostriatal Degeneration	Neuro-transmission	Behavioral Deficits	Inflammatory Signature	Other
Mouse	Striatum	1, 3, 6 months	-Global pS129 aSyn -Striatal aSyn	-TH+ Cells in SNpc -Striatal TH Intensity	-Striatal DA -Striatal DAT	-Rotarod -Wire Hang	Not Investigated	Not Investigated
Rat	Striatum	1, 2, 6 months	-Global pS129 aSyn -ThioS and PK Digestion (structures with pS129 asyn)	-TH+/NeuN+ Cells in SNpc -Striatal TH Intensity	-Striatal Monoamines and Metabolites	-Cylinder Task -Rotarod -Open Field	-Microglial Reactivity -Cytokines (STR, SN)	-LC and D Raphe Stereology if Pathology Present
Mouse: wildtype A53T SNCA -/- A30P SNCA -/-	Striatum and Hippocampus	1, 2, 6 months	-Global pS129 aSyn -Global aSyn	-TH+ Cells in SNpc	-Striatal DA	Not Investigated	-Microglia Counts -Cytokines/ Chemokines (STR, SNpc, HP, CTX)	-Bioenergetics (STR, SNpc)

Abbreviations: aSyn, alpha synuclein; TH, tyrosine hydroxylase; SNpc, substantia nigra pars compacta; DA, dopamine; DAT, dopamine transporter; ThioS, thioflavin S; PK, proteinase K; NeuN, neuronal-specific nuclear protein; STR, striatum; SN, substantia nigra; LC, locus coeruleus; D Raphe, dorsal raphe nucleus; HP, hippocampus; CTX, cortex.

Blue outcome measures have been completed: results of these experiments can be found in the 2014 Society for Neuroscience poster in the Publication page on our website.

Green outcome measures are in process and results are expected Fall 2018.

MURINE ALPHA SYNUCLEIN PFFS

Mouse and rat alpha synuclein monomers are under development at Proteos and will be made available for generation of mouse or rat PFFs when validated. The mouse and rat alpha synuclein monomers for PFF generation are expected to be available Spring 2017.

Experimental Design			Pathological Measures Investigated					
Species	Injection Site	Timepoints	aSyn Pathology	Nigrostriatal Degeneration	Neuro-transmission	Behavioral Deficits	Inflammatory Signature	Other
Rat	Striatum	2, 4, 6 months	-pS129 aSyn in SNpc -Global Oligomeric aSyn	-TH+/NeuN+ Cells in SNpc	Not Investigated	-Cylinder Task -Adjusting Steps -Open Field -Bilateral Tactile Stimulation -L-dopa Assessment	Not Investigated	-aSyn in CSF
Mouse	Striatum	3, 6 months	-pS129 aSyn in SNpc, AMYG, STR, CTX --PK digestion	-TH+/Nissl+ Cells in SNpc	Not Investigated	-Cylinder Task -Pole Test -Open Field -Wire Hang	Not Investigated	Not Investigated

Abbreviations: aSyn, alpha synuclein; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase; NeuN, neuronal-specific nuclear protein; CSF, cerebrospinal fluid; AMYG, amygdala; STR, striatum; CTX, cortex; PK, proteinase K.

Green outcome measures are in process and results are expected Spring-Fall 2018.

OUTCOME MEASURES NOT CURRENTLY UNDER INVESTIGATION

Although we are currently working to characterize the pathology of the alpha synuclein PFF model using the outcome measures listed in the tables above, we appreciate the complexity of this model and acknowledge the need for further characterization of other pathological processes affected by the alpha synuclein PFFs. As a result, we encourage scientists to continue these efforts and share their results with the research community.

ADDITIONAL INFORMATION

For additional information on the characterization work completed, please see the human alpha synuclein PFF data presented in our 2014 Society for Neuroscience poster, located in the Publications page on the MJFF website. We will provide the community with the results of the outcome measures currently under investigation when they become available in 2018. Please contact tools@michaeljfox.org with additional questions.