THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

ALPHA-SYNUCLEIN (ASYN)

As one of the hallmarks of Parkinson's disease, alpha-synuclein (aSyn) pathology is a highly desired readout in model systems. There are many models available that use aSyn mutations, overexpression, or misfolding to trigger pathology, degeneration, and behavioral readouts. Below you will find a list of commonly used aSyn-driven models of Parkinson's disease. Please note, this list is by no means comprehensive--others are available that may suit your needs. An aggregated list of transgenic synuclein models can be found here.

AAV ASYN MODEL

- Description: This model uses intranigral injection of an adeno-associated virus overexpressing wild-type or A53Tmutant aSyn into the mouse or rat. Using a high dose of a well-validated viral vector you can expect to achieve progressive loss of the nigrostriatal system that begins with dysfunction of the axon terminals in the striatum and leads to loss of the dopaminergic neurons in the substantia nigra pars compacta (generally up to ~60% loss). Motor dysfunction occurs in this model when robust cell loss is present, and inflammation is observed across studies.
- Recommended Use: Pathology in this model is driven by aSyn overexpression and is restricted to the site of injection. This model is recommended for researchers that want nigrostriatal degeneration and motor deficits. It can also be used when inflammation is desired in the model system. Users may also choose to inject a lower dose of the AAV aSyn to develop a model with a protracted time course or cell dysfunction without overt neurodegeneration.
- Helpful Resources:
  - Commercial AAV aSyn sources – MJFF Products at Charles River Laboratories
  - CRO Recommendations – Atuka, Charles River Labs
  - Review - Huntington, TE, and R Srinivasan. (2021). *Aging Dis,* 12(4): 1120-1137.

ASYN PFF MODEL

- Description: This model uses intrastriatal injection of recombinant aSyn amyloid that are 50nm or smaller (known as preformed fibrils or PFFs) into the mouse or rat. Injection of these PFFs results in templating of the endogenous synuclein to induce pathological modifications. aSyn inclusions appear in the substantia nigra pars compacta, cortex, amygdala and thalamus, brain regions with Lewy pathology in PD. The model displays a protracted timecourse with loss of axon terminals in the striatum by six weeks post-injection and loss of the dopaminergic neurons in the substantia nigra pars compacta at 3-6 months post-injection. Motor dysfunction is generally not a reliable readout in this model as cell loss in the nigra does not reach the threshold for motor impairments.
- Recommended Use: Pathology in this model is driven by pathological changes in the endogenous aSyn protein. This model is recommended for researchers that are looking to observe aSyn pathology in multiple brain regions and avoid aSyn overexpression but still observe synuclein pathology and nigrostriatal dysfunction. The model is ideal for researchers looking for a model of aSyn seeding in which an intervention can be applied while aSyn pathology is present but before degeneration. The model is not ideal for fast timelines or motor deficits.
- Helpful Resources:
  - Commercial aSyn PFF sources – MJFF aSyn PFFs (sold as monomer) or StressMarq aSyn PFFs.
  - CRO Recommendations – Atuka, Psychogenics
  - Review of PFF Model Phenotypes – Polinski, NK. (2021). *J Parkinsons Dis,* 11(4): 1555-1567.
  - Best Practices when Using aSyn PFFs – Polinski et al. (2018). *J Parkinsons Dis,* 8(2): 303-322.

ICON KEY

Protein Expression Level			Protein/Gene Species		Mutation	Pathology				
Endogenous Expression	Over-expression	Knockout	Human	Rodent	Mutant	Nigrostriatal Degeneration	Nigral aSyn Pathology	Inflammation	Motor Impairments	Cognitive Impairments

THY1 ASYN MASLIAH "LINE 61"

- Description: This transgenic mouse model overexpresses human wildtype aSyn under the Thy1 promotor. The model displays robust aSyn pathology, primarily in the cortex and limbic system. Loss of dopaminergic terminals in the striatum, motor and nonmotor dysfunction, and inflammation occurs in this model but not until late timepoints. However, the line does not display loss of neurons in the substantia nigra.
- Recommended Use: Pathology in this model is driven by high levels of aSyn overexpression (~1.5-3.5 fold). The model is recommended for researchers who want a transgenic mouse to study synuclein pathology and resulting nonmotor and motor deficits (although the motor deficits are not driven by nigral degeneration). The model is not ideal for those who want fast timelines.
- Helpful Resources:
  - Model information at Alzforum and JPND
  - CRO Recommendations – Psychogenics, QPS Austria
  - Commercial Availability – Not available. A similar line (MJFF Thy1 aSyn Line 15) is available at JAX but does not display the phenotypes of Line 61.

"M83" HUMAN A53T ASYN MOUSE

- Description: This transgenic mouse model overexpresses human A53T mutant aSyn under the prion promotor. Homozygous mice display robust aSyn pathology and motor dysfunction (paralysis). However, the dopaminergic neurons of the substantia nigra do not display aSyn pathology and do not degenerate. The motor dysfunction is thought to be caused by aSyn pathology in the spinal cord.
- Recommended Use: Pathology in homozygous mice is driven by high levels of aSyn overexpression (~4.5-fold in cortex and 28-fold in spinal cord). The model is recommended for researchers who want a transgenic mouse to study synuclein pathology and motor deficits (although the deficits are not driven by nigral cell loss). It is important to consider that the A53T aSyn mutation is very rare and does not model idiopathic PD.
- Helpful Resources:
  - Model information at JPND
  - Commercial Availability – this line is available at JAX (#004479)

"SNCA-OVX" HUMAN WT ASYN WITHOUT MURINE *SNCA*

- Description: This mouse model uses a BAC construct to express the full human wildtype *SNCA* locus with endogenous promotor on a line that lacks the endogenous mouse aSyn. Homozygous mice display age-related accumulation of aSyn pathology with early striatal signal deficits followed by nigral neuron loss and motor dysfunction at late timepoints (~18 months).
- Recommended Use: Pathology in homozygous mice is driven by moderate levels of aSyn overexpression (~1.6-fold). The model is recommended for researchers who want a transgenic mouse to study synuclein pathology and nigrostriatal degeneration resulting from human WT synuclein without the presence of the mouse aSyn protein. In addition, given that the model expresses the full human *SNCA* transgene, it is suitable for aSyn-targeted antisense oligonucleotide studies.
- Helpful Resources:
  - Model information – Janezic et al. (2002). *PNAS,* 110(42): E4016-4025.
  - Commercial Availability – this line is available at JAX (#023837)

ICON KEY

Protein Expression Level			Protein/Gene Species		Mutation	Pathology				
Endogenous Expression	Over-expression	Knockout	Human	Rodent	Mutant	Nigrostriatal Degeneration	Nigral aSyn Pathology	Inflammation	Motor Impairments	Cognitive Impairments