

## MOTOR DYSFUNCTION

Parkinson's disease (PD) is classified as a movement disorder due to the predominant issues in tremor, gait, balance, and bradykinesia. These symptoms are linked to loss of dopamine neurons in the substantia nigra and their projections to the striatum. Pathologically, abnormal alpha-synuclein (aSyn) phosphorylation and aggregation are presumed to cause this nigrostriatal degeneration. Below you will find a summary of models that display robust dysfunction. Please note, this list is not comprehensive as there are many reports of motor dysfunction in models (albeit some are subtle, not as easily replicated across labs, or the result of degeneration outside of the nigrostriatal system).

### MPTP MODEL

- **Description:** MPTP is a toxin administered to mice that acts as a mitochondrial complex I inhibitor with high affinity for the dopamine transporter. There are different dosing paradigms for MPTP that result in different pathology:
  - The acute dosing paradigm (4 administrations in 24 hours) produces rapid loss of nigral dopamine neurons and decreased dopaminergic terminals in the striatum. GI dysfunction is also present. aSyn pathology is not observed under this MPTP paradigm. Robust bilateral motor deficits occur in the days post-MPTP administration but motor recovery is observed at longer post-injection intervals.
  - Sub-acute (1 administration daily for 5-7 days) and chronic (1 administration daily for 14-28 days) dosing paradigms result in delayed nigrostriatal degeneration with accompanying aSyn pathology, neuroinflammation, GI dysfunction, and cognitive impairment. While some have reported motor deficits under these injection paradigms, others have failed to observe motor dysfunction.
- **Recommended Use:** The ability to administer MPTP through peripheral injection is a benefit of this model as it avoids the need for stereotaxic surgery. The robust motor deficits at early timepoints in the acute paradigm make this a rapid model for motor phenotypes. Caution should be taken if pursuing the subacute or chronic paradigms for motor dysfunction. This model isn't preferred for studying the impact of aSyn-related interventions on motor dysfunction. Note that mice and primates (including humans), but not rats, efficiently convert MPTP to its active metabolite, MPP+. Thus, rats are not compatible with this model and great care is imperative for the safe handling and disposal of MPTP.
- **Helpful Resources:**
  - CRO Recommendations for the MPTP Model - [Atuka](#), [Charles River Labs](#), [Psychogenics](#)

### 6-OHDA MODEL

- **Description:** 6-OHDA is a mitochondrial complex I and IV inhibitor that is administered through stereotaxic injection into the rat brain via the striatum, substantia nigra, or medial forebrain bundle (MFB). The route of administration affects pathology in this model – nigral or MFB injection will result in loss of nigral dopamine neurons followed by degeneration of striatal terminals within days, whereas striatal injection results in a progressive model that begins with degeneration of striatal dopamine terminals and results in loss of nigral dopamine neurons in a matter of weeks. Robust unilateral motor deficits are present and can appear in a manner of days or weeks, depending on the injected structure. As injections are typically unilateral, behavioral readouts typically focus on motor asymmetry. These phenotypes are reversible by L-Dopa and L-Dopa-induced dyskinesias can be triggered in the 6-OHDA model. Neuroinflammation, cognitive impairment, and GI dysfunction have also been reported in this model as well. aSyn pathology, however, is not present.
- **Recommended Use:** 6-OHDA is a potent inhibitor of mitochondrial respiration complexes I and IV. The robust degeneration and motor deficits make this an attractive model. This model isn't preferred for studying the impact of aSyn-related interventions on motor dysfunction as aSyn pathology is absent in this model.
- **Helpful Resources:**
  - CRO Recommendations for the 6-OHDA Model - [Atuka](#), [Charles River Labs](#), [Psychogenics](#)

#### ICON KEY

Model Properties			Pathology			
 Inducible	 Constitutive Expression/Knockout	 Nigrostriatal Degeneration	 $\alpha$ -Synuclein Pathology	 Inflammation	 Motor Impairments	 Cognitive Impairments

## AAV ASYN MODEL

- **Description:** This model uses intranigral injection of an adeno-associated virus overexpressing wild-type or A53T mutant 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). Injecting a well-validated AAV aSyn viral vector at a high titer can result in reliable motor dysfunction generally around 1-3 months post-injection (depending on aSyn expression level achieved). As injections are typically unilateral, behavioral readouts typically focus on motor asymmetry. Inflammation is also observed in this model.
- **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 driven by aSyn. For motor dysfunction, the rat AAV aSyn model generally produces more robust phenotypes as compared to the mouse model. The rat AAV aSyn model is also useful for deep brain stimulation experiments.
- **Helpful Resources:**
  - Commercial AAV aSyn sources – [MJFF Products at Charles River Laboratories](#)
  - CRO Recommendations – [Atuka, Charles River Labs](#)
  - Review - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8219504/>

## MITOPARK MOUSE MODEL

- **Description:** The MitoPark model involves homozygous knockout of *Tfam* specifically in midbrain dopaminergic neurons, resulting in impairments in mtDNA maintenance and the mitochondrial respiratory chain. This model displays progressive loss of dopaminergic neurons in the nigra starting at 3 months, corresponding to a progressive loss of striatal dopamine neuron terminals. Motor deficits appear at 3 months of age and continue throughout the lifespan. Synuclein inclusions are observed in dopamine neurons beginning at 1.5 months. GI pathology and dysfunction are also prevalent in this line and appear prior to motor symptoms.
- **Recommended Use:** This model is attractive in that presents with aSyn pathology, nigrostriatal degeneration, and motor dysfunction at early time points. It is important to note that the model does not necessarily reflect the pathogenic mechanisms of PD and may fail to recapitulate changes in other pathways that are important in disease.
- **Helpful Resources:**
  - Summary of Line Phenotypes – [JPND Model Summary](#)
  - Commercial Availability – This model is not commercially available.

## THY1 ASYN MASLIAH "LINE 61"

- **Description:** This transgenic mouse model overexpresses human wildtype *SNCA* under the Thy1 promotor. The model displays robust aSyn pathology, primarily in the cortex and limbic system. Loss of dopaminergic terminals in the striatum and inflammation occurs in this model at late timepoints. The line does not display loss of neurons in the substantia nigra. Regardless, motor symptoms are present in the model starting as early as 1 month of age. Deficits increase with age and this line displays impairments in multiple functional assays of motor coordination, balance and strength by 3 months. This model also displays impairments in GI function, sleep, cognition, and olfaction.
- **Recommended Use:** Pathology in this model is driven by aSyn overexpression (~1.5-3.5 fold). The model is recommended for researchers who want a transgenic mouse to study synuclein pathology or nonmotor/motor deficits driven by aSyn overexpression. This model is not ideal for looking at nigrostriatal degeneration.
- **Helpful Resources:**
  - Model information at [Alzforum](#) and [JPND](#)
  - CRO Recommendations – [Psychogenics, QPS Austria](#)
  - Commercial Availability – Not available. [MJFF Thy1 aSyn Line 15](#) is available at JAX but shows no phenotypes.

### ICON KEY

Model Properties			Pathology			
 Inducible	 Constitutive Expression/Knockout	 Nigrostriatal Degeneration	 α-Synuclein Pathology	 Inflammation	 Motor Impairments	 Cognitive Impairments

## ROTENONE MODEL

- **Description:** Rotenone is a toxic pesticide that inhibits mitochondrial complex 1 to produce degeneration when administered to mice and rats. Phenotypes vary based on route of administration and dose, but chronic, systemic administration results in loss of dopaminergic neurons in the substantia nigra,  $\alpha$ Syn pathology and inflammation. This model displays robust motor deficits in the chronic dosing paradigm. Nonmotor symptoms include GI dysfunction, sleep dysfunction, mood issues, and cognitive dysfunction.
- **Recommended Use:** The nigrostriatal degeneration,  $\alpha$ Syn pathology, motor, and nonmotor deficits make this an attractive model. It should be noted that there is substantial variability in this model and rotenone can be lethal to rodents. Also, it is important to note that the rotenone model does not necessarily reflect the pathogenic mechanisms of PD. For instance, rotenone causes microtubule destabilization which is not thought to be a key driver of PD pathophysiology. Given the toxicity of rotenone, great caution should be taken when handling this pesticide.
- **Helpful Resources:**
  - o CRO Recommendations for the Rotenone Model – [Transpharmation](#)
  - o Review of the Rotenone Model - <https://www.mdpi.com/2673-4087/1/1/1>

### ICON KEY

Model Properties			Pathology			
 Inducible	 Constitutive Expression/Knockout	 Nigrostriatal Degeneration	 $\alpha$ -Synuclein Pathology	 Inflammation	 Motor Impairments	 Cognitive Impairments