THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

MITOCHONDRIAL DYSFUNCTION

Mitochondrial function is a pathway of great interest for Parkinson's disease (PD) research and therapeutic development given the dysfunction that has been observed in idiopathic patients, patients with mutations in *parkin/PINK1* genes, and mechanism of action for known environment toxins linked to PD. Mitochondrial dysfunction is observed in many PD models. Below you will find a summary of models that use mitochondrial dysfunction to drive pathology. Please note, this list is not comprehensive.

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, leading to bilateral degeneration of dopaminergic neurons such as those in the substantia nigra. In this model, MPTP is converted to MPP+ by astrocytes, which accumulates in dopamine neurons, causing mitochondrial dysfunction. Note that mice and primates (including humans), but not rats, efficiently convert MPTP to its active metabolite, MPP+. Thus, rats are not recommended for use with this model and great care is imperative for the safe handling and disposal of MPTP to avoid permanent MPTP-induced parkinsonism in humans. There are multiple different dosing paradigms for MPTP resulting in different pathology:
  - The acute dosing paradigm (4 administrations in 24 hours) is the most common, and produces rapid loss of nigral dopamine neurons and decreased dopaminergic terminals in the striatum, stabilizing at 7 days post-injection. This lesion leads to robust motor deficits but recovery is observed at longer post-injection intervals. Alpha-synuclein (aSyn) pathology is not observed.
  - Sub-acute (1 administration daily for 5-7 days) and chronic (1 administration daily for 14-28 days) dosing paradigms are also used. These paradigms result in delayed nigrostriatal degeneration but exhibit accompanying aSyn pathology and neuroinflammation. These paradigms do not result in robust motor deficits, as some report phenotypes while others do not. Some have reported non-motor phenotypes like olfactory deficits, cognitive issues, anxiety, depression, and gastrointestinal 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. However, it is important to note that the MPTP model does not necessarily reflect the pathogenic mechanisms of PD and may fail to recapitulate changes in other pathways that are important in human disease. MPTP cannot be used in rats.
- Helpful Resources:
  - CRO Recommendations for the MPTP Model - Atuka, Charles River Labs, Psychogenics
  - Example MPTP Model Review - https://pubmed.ncbi.nlm.nih.gov/33357211/
  - Thorough characterization of chronic MPTP model - https://pubmed.ncbi.nlm.nih.gov/33519420/

6-OHDA MODEL

- Description: 6-OHDA is a mitochondrial complex I and IV inhibitor that is typically administered through stereotaxic injection into the rat brain via unilateral injection to 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. Regardless of injected structure, robust unilateral motor deficits are present and neuroinflammation is observed. aSyn pathology, however, is not present in this model.
- 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. However, it is important to note that the 6-OHDA model does not necessarily reflect the pathogenic mechanisms of PD and may fail to recapitulate changes in other pathways that are important in human disease (such as aSyn pathology).

ICON KEY

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

- Helpful Resources:
  - CRO Recommendations for the 6-OHDA Model - Atuka, Charles River Labs, Psychogenics
  - Example 6-OHDA Model Review - https://link.springer.com/article/10.1007/BF03033565

MCI-PARK MOUSE MODEL

- Description: The MCI-PARK model involves homozygous knockout of *Ndufs2* specifically in dopaminergic neurons, resulting in mitochondrial complex I inhibition in this model. Motor deficits are present in this model at early time points, starting with Levodopa-responsive phenotypes in the adhesive removal task at 30 days of age, open field test at 60 days of age, and gait abnormalities at 100 days of age. Dopamine neurochemistry deficits are present starting at 30 days of age and by 4-5 months of age approximately 40% of nigral dopamine neurons are lost.
- Recommended Use: Similar to the MPTP and 6-OHDA models, degeneration in this mouse results from inhibition of mitochondrial complex I. The benefit of this model is that no neurotoxin injection is involved so safety concerns and injection artifacts are avoided. The robust degeneration and early motor deficits make this an attractive model for testing mitochondria-target therapeutics. However, 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 human disease.
- Helpful Resources:
  - Publication on Model Characterization – https://pubmed.ncbi.nlm.nih.gov/34732887/
  - Commercial Availability – This model is available at JAX (ID 036313).

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 shows early signs of brain degeneration, with ~40% loss of dopaminergic neurons in the nigra at 3 months and up to 90% loss at 11 months. This corresponds to progressive loss of striatal dopamine neuron terminals and dopamine levels from 1.5-10 months of age. Levodopa responsive motor deficits appear at 3 months of age, with reports of decreased locomotion at 3 months, tremors and limb rigidity at 5 months, and significant locomotor decrease at 6 months. Non-motor deficits are also reported, including cognitive impairment at 2+ months and depressive symptoms at 7.5 months. Synuclein inclusions are observed in dopamine neurons from 1.5-11 months.
- Recommended Use: The early, profound pathology in this model makes it attractive for groups looking at mitochondria-target therapeutics. However, 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 human disease. In addition, enlarged brain ventricles and reduced brain volume are also observed at 30 weeks and decline in health necessitating sacrifice at 45 weeks, indicating substantial pathology that may not be PD-related.
- Helpful Resources:
  - Summary of Line Phenotypes – https://neurodegenerationresearch.eu/models-for-parkinsons-disease/in-vivo-mammalian-models/mitopark-mouse/mitopark-mouse-2/
  - Review of the MitoPark model - https://pubmed.ncbi.nlm.nih.gov/33753138/
  - Commercial Availability – This model is not commercially available.

ICON KEY

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