THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

MOOD/NEUROPSYCHIATRIC DYSFUNCTION

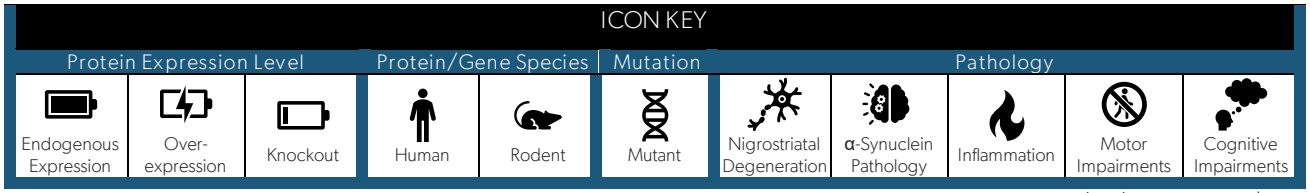
Mood issues such as depression, anxiety, and apathy are common non-motor symptoms of Parkinson's disease (PD). Some reports suggest that up to 90% of patients experience at least one of these conditions during some stage of disease, greatly reducing the quality of life of people with Parkinson's disease. Anxiety and depression can begin early in disease and continue through to late stage. These nonmotor symptoms are linked to dysfunction in noradrenergic (depression and anxiety), serotoninergic (depression and anxiety), and dopaminergic (apathy) systems. Psychosis is another symptom that has been reported in PD, particularly at later stages of disease. Below you will find a summary of models that display altered mood phenotypes. Please note, this list is not comprehensive.

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. Motor phenotypes can be induced in the model and inflammation has been reported. aSyn pathology, however, is not present. For studying neuropsychiatric symptoms, bilateral injection into the nigra or striatum results in anxiety phenotypes in the elevated plus maze, light/dark test, and open field. Depressive phenotypes have also been reported in the forced swim test and apathy was detected in sucrose preference test.
- Recommended Use: The robust degeneration and motor deficits make this an attractive model. The model can be tuned to generate full nigral lesions or partial lesions. In the context of studying neuropsychiatric symptoms, partial lesions are preferred so motor deficits do not confound nonmotor assessments. MFB injections do not result in consistent neuropsychiatric phenotypes. It is important to note, however, 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).
- Helpful Resources:
  - CRO Recommendations for the 6-OHDA Model - Atuka, Charles River Labs, Psychogenics
  - Example 6-OHDA Depression/Apathy Review - https://pubmed.ncbi.nlm.nih.gov/35645772/

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, aSyn pathology, inflammation, and motor dysfunction. Depressive and anhedonia symptoms have been reported in this model as assessed by the forced swim test and sucrose preference test. Anxiety has also been observed in the elevated plus maze. Other non-motor symptoms are also present, including sleep dysfunction, GI dysfunction, and cognitive dysfunction.
- Recommended Use: The nigrostriatal degeneration, aSyn 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. For GI studies, systemic injection seems to be more reproducible than oral administration.
- Helpful Resources:
  - CRO Recommendations for the 6-OHDA Model – Transpharmation
  - Review of the Rotenone Model - https://www.mdpi.com/2673-4087/1/1/1



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. There are multiple different dosing paradigms for MPTP resulting in different pathology, but sub-acute (1 administration daily for 5-7 days) and chronic (1 administration daily for 14-28 days) dosing are more often employed for nonmotor phenotypes. These paradigms result in delayed nigrostriatal degeneration with accompanying aSyn pathology and neuroinflammation. Motor deficits are variable in these paradigms, as some report phenotypes while others do not. Multiple groups have reported depressive symptoms in the subacute and chronic dosing regimen using tail suspension test and forced swim test, apathy in the sucrose preference test, and anxiety in the open field test and elevated plus maze. Other non-motor symptoms like olfactory deficits, cognitive dysfunction and GI dysfunction have also been reported.
- Recommended Use: The ability to administer MPTP through peripheral injection is a benefit of this model as it avoids the need for stereotaxic surgery. For mood-related phenotypes, the subacute and chronic paradigms seems more reliable, and behaviors should ideally be assessed in the absence of motor dysfunction to avoid confounds. 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. 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.
- Helpful Resources:
  - CRO Recommendations for the MPTP Model - Atuka, Charles River Labs, Psychogenics
  - Example MPTP Depression/Apathy Review - https://pubmed.ncbi.nlm.nih.gov/35645772/

BAC HU WT ASYN RAT MODEL

- Description: This rat model uses a BAC construct to express the full human wildtype *SNCA* locus, inclusive of introns, exons, promoter, and regulatory elements. The result is 2-3x overexpression of human WT aSyn in regions with endogenous expression. Homozygous rats display an age-related increase in aSyn pathology that results in nigrostriatal dysfunction and degeneration at 12+ months of age. Behaviorally, these rats display olfactory dysfunction at 3 months, anxiety phenotypes beginning at 6 months, locomotor deficits at 12 months, and male rats display psychosis-like behaviors beginning at 3 months of age.
- Recommended Use: Pathology in homozygous rats is driven by moderate levels of aSyn overexpression (2-3-fold) and resulting aSyn aggregation and truncation. The model is recommended for researchers who want a transgenic rat to study synuclein pathology and psychosis phenotypes. Long timepoints are needed if analyzing nigrostriatal degeneration or motor deficits.
- Helpful Resources:
  - Publications on development and phenotypes - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3572936/ and https://pubmed.ncbi.nlm.nih.gov/33200461/

ICON KEY

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