THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

OLFACTORY DEFICITS

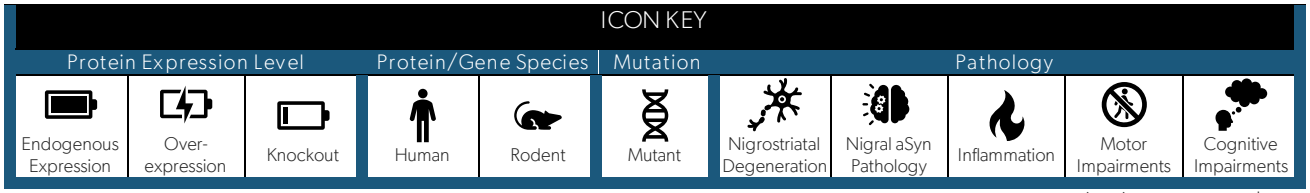
Olfactory dysfunction is a common issue in Parkinson's disease (PD), affecting 70-95% of patients. Symptoms include impairments in odor detection, identification, and discrimination. Interestingly, olfactory dysfunction can present years before motor symptoms, and individuals who have hyposmia and a relative with PD are at greater risk for developing the disease. Below you will find a list of models that display olfactory deficits. Please note, this is not comprehensive.

OLFACTORY BULB ASYN PFF MODEL

- Description: This model uses injection of recombinant aSyn amyloid that are 50nm or smaller (known as preformed fibrils or PFFs) into the mouse olfactory bulb. Injection of these PFFs results in templating of the endogenous synuclein to induce pathological modifications in the olfactory bulb and anatomically connected regions. aSyn inclusions and phosphorylation appear at 30 days post-injection with associated deficits in odor retention. Odor detection deficits appear at 3 months post-injection. Cell loss is observed in the accessory olfactory nucleus at 6 months post-injection; there is no cell loss in the olfactory bulb. The nigrostriatal system remains intact and no motor deficits are present. Inflammation is not observed.
- 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 olfactory 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 nigrostriatal/motor deficits.
- Helpful Resources:
  - Commercial aSyn PFF sources – MJFF aSyn PFFs (sold as monomer) or StressMarq aSyn PFFs.
  - CRO Recommendations – Atuka, Psychogenics
  - Review of Model Phenotypes (Table 4) – https://pubmed.ncbi.nlm.nih.gov/34486988/
  - Best Practices when Using aSyn PFFs – https://pubmed.ncbi.nlm.nih.gov/29400668/

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 systems but also in the olfactory bulb. Loss of dopaminergic terminals in the striatum, motor and nonmotor dysfunction, and inflammation occurs in this model but not until late timepoints. The line does not display loss of neurons in the substantia nigra. Regarding olfactory deficits, the line displays reduced odor detection and discrimination starting at 3 months of age and continuing until at least 11 months of age.
- 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.
  - Publication of Olfactory Deficits in Line 61 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108548/



"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. Regarding olfactory dysfunction, pS129 aSyn is observed in the olfactory structures beginning at 2 months of age and progressing in intensity and distribution over time. At 6 months of age, odor detection and discrimination are impaired. Cholinergic and dopaminergic changes in the olfactory bulb are observed at 10 months of age.
- 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)
  - Select Publications–https://pubmed.ncbi.nlm.nih.gov/20574962/ and https://pubmed.ncbi.nlm.nih.gov/21928152/