

INFLAMMATION

Inflammation is a pathway of great interest for Parkinson's disease (PD) research and therapeutic development given evidence of innate and adaptive immune changes in PD patients. Inflammation is also observed in many PD models. Below you will find a summary of common models used to study or intervene in inflammatory processes linked to PD. Please note, this list is not comprehensive. A recent review of inflammatory models if PD can be found [here](#).



AAV ASYN MODEL

- **Description:** This model uses intranigral injection of an adeno-associated virus overexpressing human 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). Motor dysfunction occurs in this model when robust cell loss is present. In both rats and mice injected with AAV aSyn, early microglial activation, increased pro-inflammatory cytokine expression, and T cell infiltration occur in the striatum and nigra prior to cell loss.
- **Recommended Use:** Pathology in this model is driven by aSyn overexpression and is generally restricted to the site of injection or overexpression. This is an appropriate model for studying inflammation as a consequence of alpha-synuclein pathology or potential driver for further degeneration as therapeutic strategies reducing inflammation have been shown to decrease pathology and attenuate dopaminergic cell loss.
- **Helpful Resources:**
 - Commercial AAV aSyn sources – [MJFF Products at Charles River Laboratories](#)
 - CRO Recommendations – [Atuka, Charles River Labs](#)
 - Review of AAV aSyn model phenotypes - <https://pubmed.ncbi.nlm.nih.gov/27018978/>

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:
 - The acute dosing paradigm results in rapid, substantial loss of nigral dopamine neurons and decrease in striatal terminals, stabilizing at 7 days post-injection. This lesion leads to robust motor deficits, but recovery is observed at longer post-injection intervals. aSyn pathology is not observed. This model generally displays microglial activation, astrogliosis, infiltrating T cells, and increase in pro-inflammatory cytokines in the striatum and nigra.
 - Sub-acute and chronic dosing paradigms result in delayed nigrostriatal degeneration and exhibit accompanying aSyn pathology. Robust motor deficits are not present, as some report phenotypes while others do not. Non-motor phenotypes like olfactory deficits, cognitive issues, anxiety, depression, and gastrointestinal dysfunction have also been reported. Regarding inflammation, these paradigms result in microglial activation, astrogliosis, and pro-inflammatory cytokine increases. The sub-acute model also shows NLRP3 activation.
- **Recommended Use:** In this model, MPTP is converted to MPP⁺ by astrocytes for internalization into dopamine neurons causing mitochondrial dysfunction. As such, this model is dependent on non-cell autonomous processes. This is an appropriate model for studying inflammation as a consequence of neuronal dysfunction or driver for further degeneration, as reducing inflammation can decrease pathology. Given the role of astrocytes and microglia in MPTP processing, caution should be taken if using this model to modulate the number/function of these cells.
- **Helpful Resources:**
 - CRO Recommendations for the MPTP Model - [Atuka, Charles River Labs, Psychogenics](#)
 - Example publications of inflammation in the MPTP model - <https://pubmed.ncbi.nlm.nih.gov/19286483/>, <https://pubmed.ncbi.nlm.nih.gov/19410592/>

ICON KEY

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








ASYN PFF MODEL

- **Description:** This model uses injection of recombinant mouse aSyn amyloid that are 50nm or smaller (known as preformed fibrils or PFFs) into the brain (generally striatum) of 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 time course 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 as cell loss in the nigra is quite variable (20-60%) and often does not reach the threshold for motor impairments. Regarding inflammation, there have been mixed reports of inflammation in mice injected with aSyn PFFs, with some observing microglial activation, astrogliosis, and increased cytokines while others find no evidence of inflammation. Inflammation in the rat aSyn PFF model is more consistent, with groups reporting microglial activation and infiltration of peripheral monocytes, macrophages, and T cells.
- **Recommended Use:** This model is recommended for researchers interested in understanding the relationship between inflammation and aSyn seeding, or intervening in a model that involves aSyn seeding or pathology in endogenous synuclein. As many groups have struggled to observe inflammation in mice injected with aSyn PFFs, it is recommended to use PFF injection in rat or perform a pilot study in mice to ensure inflammation is present. If using the aSyn PFF model to study inflammation, the monomeric aSyn is recommended as a control and you must ensure that your protein (monomeric and PFF) has low/no endotoxin.
- **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 – <https://pubmed.ncbi.nlm.nih.gov/34486988/>
 - Best Practices when Using aSyn PFFs – <https://pubmed.ncbi.nlm.nih.gov/29400668/>

LPS MODEL

- **Description:** The administration of lipopolysaccharide (LPS) has long been a method to induce inflammation. LPS has been delivered through intraperitoneal injection, intranasal injection, and intranigral/striatal injection to trigger nigrostriatal degeneration and inflammation in mice and rats. Regardless of route of administration, LPS induces loss of nigral dopamine neurons, increase microglial activation in the substantia nigra, increase in pro-inflammatory cytokine production, and astrogliosis. T cell infiltration does not occur in this model. LPS models also commonly report motor deficits resulting from the nigrostriatal degeneration, non-motor phenotypes such as GI dysfunction and cognitive issues, and aSyn pathology.
- **Recommended Use:** The LPS model is a “sledgehammer” model whereby huge inflammatory changes/cascades are initiated through LPS administration. However, it is a strong model for non-cell autonomous and innate immune mechanisms of nigral degeneration given that TLR4 (the receptor for LPS) is not expressed on neurons. This model does not exhibit adaptive immune responses and should not be used to study that aspect of inflammation. While the LPS model is a good for studying extreme inflammation leading to nigrostriatal degeneration, it should not be the only model selected for studying inflammation in PD due to severity and lack of disease relevance.
- **Helpful Resources:**
 - Review on LPS models – [Deng et al \(2020\) Brain, Behavior, and Immunity](#).

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