A Summary of Phenotypes Observed in the In Vivo Rodent Alpha-Synuclein Preformed Fibril Model

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Abstract. The use of wildtype recombinant alpha-synuclein preformed fibrils (aSyn PFFs) to induce endogenous alpha-synuclein to form pathological phosphorylation and trigger neurodegeneration is a popular model for studying Parkinson’s disease (PD) biology and testing therapeutic strategies. The strengths of this model lie in its ability to recapitulate the phosphorylation/aggregation of aSyn and nigrostriatal degeneration seen in PD, as well as its suitability for studying the progressive nature of PD and the spread of aSyn pathology. Although the model is commonly used and has been adopted by many labs, variability in observed phenotypes exists. Here we provide summaries of the study design and reported phenotypes from published reports characterizing the aSyn PFF in vivo model in rodents following injection into the brain, gut, muscle, vein, peritoneum, and eye. These summaries are designed to facilitate an introduction to the use of aSyn PFFs to generate a rodent model of PD—highlighting phenotypes observed in papers that set out to thoroughly characterize the model. This information will hopefully improve the understanding of this model and clarify when the aSyn PFF model may be an appropriate choice for one’s research.

Keywords: Alpha-synuclein, Parkinson disease, preformed fibril, model

INTRODUCTION

Parkinson’s disease (PD) is a neurodegenerative disorder affecting approximately 1% of the population over the age of 60. Characterized by motor disturbances as well as non-motor symptoms, the pathology of PD involves deposits of aggregated, phosphorylated alpha-synuclein (aSyn) protein in affected tissues and brain structures and degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Given that PD is a human-specific condition, various models have been developed to enable research and therapeutic development for this disease. Common models include injection of neurotoxins to trigger degeneration of the dopaminergic neurons of the SNpc, transgenic rodent models carrying PD-related genetic mutations, and induction of aSyn pathology through viral vector-mediated overexpression of aSyn, among others [1–3]. All models present with advantages and disadvantages, so selection of the model should be based on the desired pathology for the intended research question.

In the last 10 years, a model has arisen that capitalizes on the observations made by Braak and colleagues that aSyn pathology progressively accumulates in different brain regions following a spatiotemporal pattern that suggests spreading [4–7]. This model, dubbed the aSyn preformed fibril (PFF) model, uses injection of recombinant aSyn protein that has been stimulated to form aggregates and son-
icated to produce short fibrils [8–10]. These aSyn PFFs cause templating of endogenous aSyn into pathological species characterized by phosphorylation at S129 (pS129 aSyn), beta-sheet formation, and aggregation, followed by increases in autophagy and neuronal dysfunction [11]. The flexibility of this model allows injection of different forms of aSyn PFFs (e.g., mouse vs. human aSyn, mutated aSyn), unilateral or bilateral injection, targeting of different brain regions and administration through different peripheral routes to model distinct aspects of the disease. This flexibility is a strength of the model but also serves as a weakness, as the distinct protocols lead to different pathologies which has hampered cross-study comparisons. To better understand the various study designs employed for the aSyn PFF model and the resulting pathologies, a survey of the literature was performed and is summarized within this manuscript.

GUIDE TO READING AND INTERPRETING THE TABLES

As hundreds of studies using the aSyn PFF model have been published, Tables 1–9 herein contain information specifically from publications that sought to phenotype the effects of injection of recombinant wildtype aSyn PFFs into rodents to develop a PD model. As a result, the tables are not comprehensive in nature but do contain reports from a variety of studies across laboratories.

Studies focusing on the uptake of aSyn following injection have been excluded as the study is not designed to thoroughly assess resulting pathology. Studies using the aSyn PFF model to test the effect of an intervention have been excluded as the focus is on the therapeutic intervention tested rather than the characterization of the pathological process and timelines. Studies injecting aSyn PFFs to model another disease (e.g., Multiple System Atrophy) were excluded to focus specifically on PD. Studies injecting aSyn PFFs into non-human primates or using aSyn PFFs in cell culture were excluded for the sake of focus. Studies injecting rodent/patient brain-derived material were excluded due to concerns that the injectate is not homogenous and the concentration of aSyn and other protein components cannot be known or compared across studies. Although a number of studies have been published analyzing the differences in pathogenicity of fibrils of different conformations [12–18], different aSyn truncations [23–25], and different aSyn post-translational modifications [26], these were excluded from the summary tables as the objective of these experiments is to compare pathogenicity relative to wildtype aSyn PFFs and therefore the nuanced information requires a different venue.

Tables 1–9 are organized by categories such as: injected species (mouse vs. rat), route of administration of aSyn PFFs, and species of aSyn PFF (human vs. mouse). To understand the variation in observed phenotypes within the model, readers should compare only within categories rather than across categories. Please note that there may be differences in study design within categories (e.g., unilateral vs. bilateral injection, wildtype vs. transgenic rodent) that should be taken into account when drawing conclusions on timelines and robustness of phenotypes.

Papers included within the tables are organized chronologically, with high-level information on study design, outcome measures, and notes that may provide additional context for the reader. Information on study design includes the rodent strain used, the injectate, the dose of aSyn PFFs with information on whether this dose was administered bilaterally or unilaterally (for bilateral injections, the total dose noted was for each hemisphere), and the days post-injection (DPI) at which time the model was analyzed. Reported phenotypes are separated by category to facilitate comparisons of common readouts across studies. The time post-injection at which the phenotype was observed is included, with a “+” indicating the phenotype was also observed at the later time-points. If later timepoints were analyzed within the study but the “+” sign is absent, this indicates that either the phenotype was not analyzed at the later timepoints or was analyzed but not observed. If a phenotype was observed in a particular structure, the structure is included in parentheses. Readouts that were not included in the study are denoted as “N/A”.

Please note, to fully understand all reported or absent phenotypes in the models, a separate literature review is required.

SUMMARY OF PHENOTYPES REPORTED IN THE ASYN PFF MODEL

The earliest aSyn PFF model studies were performed by injecting aSyn PFFs into the mouse striatum. Table 1 provides a summary of studies that used unilateral or bilateral intrastriatral injection of
Table 1
Injection of mouse aSyn PFFs into the wildtype mouse striatum

| Paper | Unilateral Mouse aSyn PFFs | Bilateral Mouse aSyn PFFs |
|-------|---------------------------|---------------------------|
|      | | | Sorrentino 2017 | Stoyka 2020 | Ding 2021 |
| Rodent Strain | | | | | |
| | aSyn, alpha-synuclein; PFFs, preformed fibrils; TH, tyrosine hydroxylase; DA, dopamine; N/A, not analyzed; SNpc, substantia nigra pars compacta; STR, striatum; AMY, amygdala; ROS, reactive oxygen species. | | | |
| Luk 2012 | Masuda-Suzukake 2014 | Luk 2016 | Fares 2016 | Henderson 2019 | Izco 2020 | Burtsher 2020 | Kim 2020 |
| [27] | [28] | [19] | [29] | [30] | [31] | [32] | [33] |
| Rodent Strain | C57Bl/6C3H | C57Bl/6J | C57Bl/6C3H | C57Bl/6C3H | C57Bl/6J | C57Bl/6C3H | C57Bl/6J | C57Bl/6J |
| Injectate | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn |
| Total Dose | 5 ug (Unilateral) | 10 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) |
| DPI | 30, 90, 180 | 30, 90, 180 | 14, 30, 90, 180 | 30, 30, 90, 180 | 15, 30, 90, 180 | 30, 60, 180 | 30 | Mouse aSyn |
| | | | | | | | Mouse aSyn |
| Total Dose | 5 ug (Unilateral) | 10 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) |
| DPI | 30, 90, 180 | 30, 90, 180 | 14, 30, 90, 180 | 30, 30, 90, 180 | 15, 30, 90, 180 | 30, 60, 180 | 30 | Mouse aSyn |
| | | | | | | | Mouse aSyn |
| p562 aSyn | 30+ | 30 | 14+ | 30 | 30+ | 15+ | 30+ | 30 |
| Strial TH Loss / DA Deficits | 90+ | N/A | N/A | N/A | 90 | N/A | N/A |
| SNpc TH+ Cell Loss | 90+ | N/A | 180 | N/A | 90+ | Absent | N/A | N/A |
| Behavioral Deficits | Motor - 180 | Motor - 90 | Cogntive - Absent | Motor - 180 | Motor - 90 | Motor - 90 | N/A | N/A |
| Immune Response | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Other | N/A | Aggregated aSyn - 90 | Tau Pathology - 30 | Aggregated aSyn - 90 | Ubiquitinated | Inclusions - 30 | N/A | N/A |
| | | | | | | | | | | |
| | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| | | | | | | | | Pathology absent with injection of human aSyn PFFs |
| Note | CD1 and B6SJL rodent strains also assessed | Injected human aSyn PFFs and saw little pathology | Analyzes spread patterns and regional vulnerabilities | Pathology worse when meningeal lymphatic drainage blocked | N/A | N/A | N/A | N/A |

aSyn, alpha-synuclein; PFFs, preformed fibrils; TH, tyrosine hydroxylase; DA, dopamine; N/A, not analyzed; SNpc, substantia nigra pars compacta; STR, striatum; AMY, amygdala; ROS, reactive oxygen species.
Table 2
Unilateral injection of human aSyn PFFs into the wildtype mouse striatum

| Paper | Luk 2016 [19] | Fares 2016 [29] | Milanese 2018 [37] |
|-------|---------------|----------------|-------------------|
| Rodent Strain | C57B16/C3H | C57B16/C3H | C57B16/6 |
| Injectate | Human aSyn | Human aSyn | Human aSyn |
| Total Dose | 5 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) |
| DPI | 14, 30, 90, 180 | 30 | 120 |
| pS129 aSyn | 30+ | 30 | 120 |
| Striatal TH Loss / DA Deficits | N/A | N/A | 120 |
| SNpc TH+ Cell Loss | Absent | N/A | 120 |
| Behavioral Deficits | Absent | N/A | N/A |
| Immune Response | N/A | N/A | N/A |
| Other | Aggregated aSyn - 90 | N/A | DNA Damage (SN) - 120 |

Note: Also tested chimeric human-mouse aSyn PFFs. Homology to mouse aSyn increased pathology. Injected mouse aSyn PFFs. Pathology with mouse aSyn PFFs greater than human aSyn PFFs.

Table 3
Unilateral and bilateral injection of aSyn PFFs into transgenic mouse striatum

| Paper | Luk 2012 [23] | Sorrentino 2017 [34] | Earls 2020 [38] | Blumenstock 2017 [39] | Hendersin 2019 [40] | Bieri 2019 [40] | Migdalaska-Richards 2020 [41] |
|-------|---------------|----------------|----------------|-----------------|----------------|----------------|----------------|
| Rodent Strain | M38 AS3T Hu aSyn | M20 WT Hu aSyn | M38 AS3T Hu aSyn | Thy-1 eGFP | BAC LRRK2 G0195S | BAC LRRK2 G0195S | GBA L444P KI |
| Injectate | Human aSyn | Human aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn |
| Total Dose | 5 ug (Unilateral) | 4 ug (Unilateral) | 4 ug (Unilateral) | 5 ug (Unilateral) | 25 ug (Unilateral) | 5 ug (Unilateral) | 5 ug (Unilateral) |
| DPI | 90 | 120 | 120 | 70 | 30, 60, 90, 150, 270 | 30, 90, 180 | 30, 90, 180 | 120 |
| pS129 aSyn | 90 | 120 | 120 | 70 | 30+ | 30+ | 120 |
| Striatal TH Loss / DA Deficits | N/A | N/A | N/A | Absent | N/A | N/A | N/A |
| SNpc DA Cell Loss | N/A | N/A | N/A | Absent | N/A | N/A | 90+ | 180 | N/A |
| Behavioral Deficits | N/A | N/A | N/A | Motor - 70 | N/A | Motor - 90+ | Motor - 180 | N/A |
| Immune Response | N/A | Microglia Activation - 120 | Microglia Activation - 120 | Microglia Activation - 150 (variable) | N/A | Microglia Activation - 180 | N/A |
| Other | N/A | N/A | N/A | Aggregated aSyn - 70 | N/A | N/A | N/A |

Note: Also injected truncated AA1-120 human aSyn PFFs. Tested different injection coordinates. NK cell depletion worsened pathology. Pathology in LRRK2 G0195S mouse worse than WT. Pathology in LRRK2 G0195S mouse worse than WT. Pathology in GBA L444P mouse worse than WT.

aSyn, alpha-synuclein; PFFs, preformed fibrils; Hu, human; TH, tyrosine hydroxylase; DA, dopamine; N/A, not analyzed; SNpc, substantia nigra pars compacta; CPu, caudate putamen; CTX, cortex.
Table 4

Unilateral and bilateral injection of αSyn PFFs into the wildtype and transgenic mouse olfactory bulb or sublaterodorsal tegmental nucleus

| Paper          | Olfactory Bulb | Sublaterodorsal Tegmental Nucleus [SLD] |
|----------------|----------------|----------------------------------------|
| Rodent Strain |                |                                        |
| C57Bl/6       | C57Bl/6        | BAC Hu AS3 αSyn Mouse                  |
| Mouse αSyn    | Human αSyn     | Mouse αSyn                              |
| 4 ug (Unilateral) | 4 ug (Unilateral) | 2.5 ug (Bilateral)                     |
| DPI           | 30, 90, 180, 360 | 60, 180, 210, 240, 300                |
| αSyn, αSyn    | αSyn           | Mouse αSyn                              |
| 30+           | 300            |                                        |
| Cell Loss     | Absent (OB)    | Absent (OB)                             |
| Behavioral    | Anxiety - 30   | Motor - 150                             |
| Immune        | Microglia      | Microglia                              |
| Response      | Microglia      | Microglia                               |
| Other         | Aggregated αSyn 30 | Aggregated αSyn 60                    |
| Note          | Mouse αSyn PFFs induced more pathology | Pooled injected & unexpected hemisphere and all brain structures |

Table 5

Unilateral or bilateral injection of αSyn PFFs into the wildtype or transgenic mouse hippocampus, cortex, or substantia nigra

| Paper          | Hippocampus | Cortex | Substantia Nigra |
|----------------|-------------|--------|------------------|
| Rodent Strain |             |        |                  |
| M20 WT Hu αSyn| C57Bl6/C3H  | C57Bl6/C3H | C57Bl6/C3H       |
| Injection     |             |        |                  |
| Human αSyn    | Mouse αSyn  | Mouse αSyn | Mouse αSyn       |
| 4 ug (Bilateral) | 5 ug (Unilateral) | 10 ug (Unilateral) |
| DPI           | 60, 120     | 90, 30 | 30, 90, 180, 450 |
| αSyn, αSyn    | αSyn        | αSyn   | αSyn             |
| 60+           | 45+         | 90     | 30               |
| Cell Loss     | Absent (HC) | N/A    | N/A              |
| Behavioral    | N/A         | N/A    | N/A              |
| Immune        | N/A         | N/A    | N/A              |
| Other         | N/A         | N/A    | N/A              |
| Note          |             |        |                  |

Others have chosen to inject non-striatal brain regions to model prodromal or non-motor features of PD in mice. Table 4 provides a summary of studies injecting αSyn PFFs into the olfactory bulb (OB) or sublaterodorsal tegmental nucleus (SLD) to model PD in mice.
A visual representation of timelines of phenotypes reported in common iterations of the aSyn PFF model is provided in Fig. 1. Replicated phenotypes that have been reported in more than one study are provided along the timeline of the model. Phenotypes that were only investigated in one study are also included but denoted as “underexplored phenotypes”. An inset containing phenotypes that were reported as absent is also included.

DISCUSSION

For all studies, one of the earliest phenotypes reported is the presence of pS129 aSyn within brain regions innervating the injected structure. As the model progresses, the density of pS129 aSyn pathology and gut-to-brain transmissibility of aSyn pathology. Importantly, the phenotypes observed in this model are not always reproducible and their presence/absence varies between studies (Fig. 1). This can be noted...
Table 7
Injection of aSyn PFFs into the wildtype or transgenic rodent gut

| Paper | Uemura 2018 [61] | Kim 2019 [62] | Uemura 2020 [63] | Challis 2020 [64] | Wang 2020 [65] | Holmqvist 2014 [66] | Manfredsson 2018 [67] | Van Den Berge 2019 [68] | Van Den Berge 2021 [69] |
|-------|-----------------|----------------|-----------------|-----------------|----------------|-------------------|-------------------|-------------------|-------------------|
| Rodent Strain | C57Bl/J | C57Bl/J | C57Bl/N (2 month) | C57Bl/N (10 month) | M83 A53T Hu aSyn | Sprague Dawley | Sprague Dawley | Sprague Dawley | Fischer 344 |
| Injectate | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Human aSyn | Human aSyn | Mouse aSyn | Human aSyn | Mouse aSyn |
| Injection Site | Gastric Wall (unclear location) | Stomach & Duodenum (gastric wall) | Pylorus & Duodenum (gastric wall) | Duodenum (gastric wall) | Duodenum (gastric wall) | Stellate ganglia, Celiac ganglia | Stomach & Duodenum (gastric wall) | Descending Colon (gastric wall) | Pylorus & Duodenum (gastric wall) |
| Total Dose | 40ug (over 8 sites) | 25ug (over 2 sites) | 48ug (over 8 sites) | 6ug (over 2 sites) | 6ug (over 2 sites) | 11ug (over 4 sites) | 15ug (over 5 sites) | 60ug (over 6 sites) | 18ug (over 6 sites) |
| DPI | 23, 45, 180 | 30, 90, 210, 300 | 30, 60, 120, 180, 240 | 7, 21, 60, 120 | 7, 21, 60, 120 | 30, 60, 120 | 150, 180, 210 | 0.5, 1, 2, 3, 6 | 30, 180, 360 |
| Peripheral Spinal Cord pS129 aSyn | 45+ (DMV) 160 (MG) | 30+ (DMV) | 30, 60 (DMV, MG) Absent in duodenum and SC | 60 (MG) Absent (DMV) | 120 (DMV) | 30+ (SC) 60+ (GI, skin, heart, sweat gland) | 2+ (vagal nerve) 6 (DMV) | 30+ (MG) 30 (DMV) | Absent |
| CNS PpS129 aSyn | Absent | 30+ (Brainstem) 90+ (Midbrain) 210+ (Forebrain) | 120 (Brainstem) Absent in Midbrain and Forebrain | Absent (Midbrain) Absent (Midbrain) | 120 (Midbrain) | 30+ (Brainstem, Midbrain) | Absent |
| Cell Loss | N/A | SNpc DA - 210+ | N/A | Absent (MG) Absent (SN) | N/A | Absent | Absent | Absent | N/A |
| Behavioral Deficits | N/A | Motor - 210+ Cognitive - 210+ Psychiatric - 210+ Offactory - 300 | N/A | Motor - 60, 90 GI - 60+ Motor - 120 GI - 120 | GI - 90 Offactory - 90+ Orthostatic hypotension - 90+ Hypoaldosteronism - 90+ | N/A | N/A | N/A | N/A |
| Other | Nitrotyrosine aSyn (DMV) - 45 | GI inflammation - 7+ | Nitrated aSyn (DMV, MG) - 30, 60 Ubiquitin and p62 (DMV, MG) - 30, 60 | Striatal DA deficits - Absent | Striatal DA deficits - 120 | N/A | N/A | N/A | N/A |
| Note | Vagotomy | No brain pathology | Patent pathology in DMV | AAV-PHP.S GCase overexpression | Reduced pathology | aSyn pathology was equal in PPF & monomer groups | Rats also injected with human S129a aSyn PFFs; pathology worse with age. Pathology with mouse PFFs greater than human PFFs. | N/A | N/A |

aSyn, alpha-synuclein; PFFs, preformed fibrils; Hu, human; DMV, dorsal motor nucleus of the vagus; MG, myenteric ganglia; SC, spinal cord; GI, gastrointestinal system; CNS, central nervous system; SNpc, substantia nigra pars compacta; DA, dopamine; KO, knockout.
Table 8
Unilateral or bilateral injection of aSyn PFFs into the transgenic mouse muscle

| Paper          | Intramuscular                                                                 |
|---------------|-------------------------------------------------------------------------------|
| Rodent Strain | Mouse  | Mouse | Mouse | Mouse | Mouse | Mouse | Mouse |
|               | M83 A53T Hu aSyn Mouse | M83 A53T Hu aSyn Mouse | M83 A53T Hu aSyn Mouse | GFP-tagged A53T SNCAl KI Mouse | M83 A53T Hu aSyn Mouse | M83 A53T Hu aSyn Mouse |
| Injectate     | Human aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn |
| Total Dose    | 10 ug  (Bilateral) | 20 ug (Bilateral) | 10 ug (Bilateral) | 10 ug (Unilateral) | 10 ug (Bilateral) | 20 ug (Bilateral) |
| DPI           | 126-160 | 134 | 30, 60, 90 | 120, 240 | 30, 90, 117 | 45 |

Table 9
Injection of aSyn PFFs into the wildtype or transgenic rodent peritoneum, vein, nerve, or eye

| Paper          | Intraperitoneal | Intravenous | Nerve | Intravitreal |
|---------------|-----------------|-------------|-------|-------------|
| Rodent Strain | Mouse aSyn | Mouse aSyn | Mouse aSyn | Mouse aSyn |
|               | M83 A53T Hu aSyn Mouse | M83 A53T Hu aSyn Mouse | Sprague Dawley Rats | M83 A53T Hu aSyn Mouse |
| Injectate     | Mouse aSyn | Mouse aSyn | Human aSyn | Mouse aSyn |
| Total Dose    | 50 ug  | 50 ug | 20 ug | 4 ug |
| DPI           | 180 | 350 | 120 | 30 |

when analyzing the phenotypes listed in Tables 1–9 when comparing studies of similar designs with regard to injection site, unilateral vs bilateral injection, wildtype vs transgenic rodent, etc.

An example of this can be found in motor deficits observed following intrastriatal injection. Despite using the same dose of aSyn PFFs, some report motor deficits following unilateral intrastriatal injection of mouse aSyn PFFs as early as 90 DPI [28, 30, 31] while others do not observe motor impairments until 180 DPI [19, 27] (Table 1). Others still do not observe motor impairments even at 180 days...
Fig. 1. Visual representation of the various phenotypes reported in common iterations of the alpha-synuclein preformed fibril (aSyn PFF) model. Replicated phenotypes (reported in > 1 study) and underexplored phenotypes (observed in only 1 study) are mapped across the timeline of the model. Phenotypes that were investigated but found to be absent are also included in an inset to the right of the table. Italicized phenotypes are those that vary across studies by either their presence/absence (denoted by superscript A) or timing of appearance (denoted with superscript T). For all italicized phenotypes, the most common time at which the phenotype is observed is reported.

following bilateral injection [35]. Some of these differences may be attributed to the behavioral assays employed. For instance, Henderson et al. (2019) used two behavioral tests in the same cohort—grip strength and rotarod—and demonstrated differences in grip strength upon aSyn PFF treatment but no effect of aSyn PFF treatment on rotarod performance [30]. These differences in detecting an effect of aSyn PFF treatment on motor function or non-motor function could be due to the physiology probed within these assays, the sensitivity of the tests, or confounds that may impact the readouts [77].

Another phenotype that greatly varies between studies is pS129 aSyn pathology in the brain following injection of aSyn PFFs to the gut (Table 7). Roughly half of the studies observe pS129 aSyn pathology spread to the midbrain/forebrain [62, 64, 65, 68] whereas the other half observe pathology in the periphery/brainstem that never progresses to the midbrain/forebrain [61, 63, 64, 66, 68]. As mentioned in a recent review by Bindas et al. (2021), the reason for this is unclear but could relate to gastrointestinal conditions, amount of pathology generated, site of pathology, and type of pathology induced by the aSyn PFFs [78].

When attempting to understand the variability within the aSyn PFF model, it is important to understand the various factors that can influence the pathogenicity of the aSyn PFFs. Some factors may be obvious and easily accounted for, such as dose or days post-injection. Other factors are not so clear. The source and method of preparing the aSyn PFFs can greatly influence their pathogenicity. Multiple studies have noted that endotoxin may impact the aSyn
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CONFLICT OF INTEREST

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CONFLICT OF INTEREST

The author has no conflicts of interest to report.

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