

Biomarker Recommendations for NLRP3 Inhibitor Trials in Parkinson's Disease

This document provides consensus biomarker recommendations for sponsors and investigators designing clinical trials of NLRP3 inflammasome inhibitors in Parkinson's Disease (PD). Although not meant to be prescriptive, recommendations included here are based on a synthesis of emerging clinical trial data, published literature, and expert input compiled by the Michael J. Fox Foundation for Parkinson's Research. Biomarkers are organized by mechanistic proximity to NLRP3: direct pharmacodynamic or target engagement markers, downstream pathway modulation markers (not specific to NLRP3 pathway activation but often used as target engagement / pharmacodynamic markers) and neurodegeneration / disease pathology biomarkers. Elevated baseline hsCRP may be used as a predictive biomarker or enrollment enrichment criterion with a pre-specified baseline threshold (e.g. >1 mg/L in ongoing DAPA-PD trial').

Recommended Biomarker Panel

Compartment

C CSF ONLY

P PLASMA ONLY

B CSF & PLASMA

I IMAGING

DIRECT

Target Engagement / Pharmacodynamic Biomarkers

B IL-1 β

B IL-18 (total & IL-18BP)

P ASC (total)

P Caspase-1 (cleaved p20)

DOWNSTREAM

Pathway Modulation / Pharmacodynamic Biomarkers

B IL-6

C CCL2 (MCP-1)

C IL-8 (CXCL8)

C TREM2

P hsCRP (enrichment potential)

P Fibrinogen

P SAA (serum amyloid A)

NEURODEGENERATION

Disease Pathology Biomarkers

B NfL

B S100B

B GFAP

B A β 40 / A β 42

B α -Synuclein (total/pS129)

C YKL-40

I TSPO PET([¹⁸F]-DPA-714)

TSPO PET recommended for mechanistic sub-studies only · Multiplexing recommended where possible to reduce sample volume requirements · Additional exploratory or discovery-focused readouts could include larger proteomic-type panels to identify novel "hits" for follow-up in future trials (e.g. NULISA CNS or inflammation panels)

Biomarker Reference Table

Category	Biomarker/Compartment	Platform	Key Findings
Direct measures	ASC (total) / plasma	ELLA	Elevated in PD plasma ^{2*}
Direct measures	Caspase-1 (p20) / plasma	ELLA	Elevated in PD plasma ^{2*}
Direct measures	IL-1 β (total) / CSF, plasma, whole blood	Simoa; MSD S-PLEX; ELLA; NULISA AQ Whole blood: ex-vivo LPS stim	Pharmacodynamic- Decreased after treatment in clinical trials ³⁻⁵ ; low detection in plasma limits utility ³⁻⁴ ; elevated in PD in published literature ⁶⁻⁷
Direct measures	IL-18 (free) / CSF, plasma	MSD U-PLEX + Quantikine ELISA or NULISA AQ (IL-18BP)	Elevated in PD at baseline ^{3*} ; Pharmacodynamic- decreased after treatment ³⁻⁴ ; strongest plasma signal among direct pathway markers

Direct measures	IL-18 (total) / CSF, plasma	MSD U-PLEX; ELLA	Reduced in CSF after treatment in one study ⁵ ; elevated in PD plasma ²
Downstream measures	hsCRP / plasma	Cobas (or equivalent)	Pharmacodynamic- Decreased after treatment in subjects with detectable baseline ³⁻⁵ ; Predictive use under investigation- >1mg/L being tested as enrollment criterion ¹ ; elevated in PD ⁸ ; strongly confounded by peripheral comorbidities
Downstream measures	Fibrinogen / plasma	Clauss method (Dade kit or equivalent)	Pharmacodynamic- Trend toward decrease after treatment ³ ; elevated in PD ^{8*}
Downstream measures	IL-6 / CSF, plasma	MSD U-PLEX; Simoa; Cobas; ELLA; NULISA AQ	Pharmacodynamic- Decreased after treatment in trials ³⁻⁴ ; elevated in PD CSF ⁷ ; CSF levels correlate with motor severity ⁹⁻¹⁰ ; one of the most consistently responsive markers across trials
Downstream measures	IL-8 (CXCL8) / CSF	MSD U-PLEX	Pharmacodynamic- Decreased after treatment ³ ; mixed findings in PD baseline ^{7,11} ; CSF sampling required
Downstream measures	MCP-1 (CCL2) / CSF	MSD U-PLEX; NULISA AQ	Pharmacodynamic- Decreased after treatment ³ ; no change in PD baseline ⁷ ; CSF more informative than plasma
Downstream measures	SAA (Serum amyloid A) / plasma	MSD U-PLEX; Cobas	Pharmacodynamic- Decreased after treatment ⁴ ; elevated in PD ⁹ ; acute reactant useful in inflammatory panel
Downstream measures	TREM2 / CSF	MSD ELISA; Lumipulse; Simoa; ELLA; NULISA AQ	Mixed results across trials possibly due to heterogeneity ^{3-4#} ; microglial activation marker; mechanistic data link NLRP3 & TREM2 ⁷
Downstream measures	TSPO PET / brain imaging	¹⁸ F-DPA-714 PET	Mixed results across trials ^{4-5#} ; microglial activation marker; high cost & site burden so likely most useful for mechanistic sub-studies
Neurodegeneration	NfL / CSF, plasma	Simoa; ELLA	Reduced in subset after treatment ³ ; elevated in PD CSF ⁷ ; plasma less sensitive for short-term changes ⁴ ; axonal injury marker; short trials unlikely to show change [#]
Neurodegeneration	GFAP / CSF, plasma	Simoa; ELLA; Lumipulse	Unchanged in trial data ⁴ ; astrocyte marker; short trials unlikely to show change [#]



Neurodegeneration	S100B / CSF, plasma	Cobas (or equivalent)	Unchanged in trial data ⁴ ; elevated in PD CSF ⁷ ; astrocyte/glial marker; short trials unlikely to show change [#]
Neurodegeneration	YKL-40 / CSF	Simoa; MSD U-PLEX/V-PLEX; ELLA; Quantikine; NULISA AQ	Mixed findings in PD baseline ^{7,9} ; elevated baseline predictive of developing dementia ¹²⁻¹³ ; glial activation marker; short trials unlikely to show change [#]
Neurodegeneration	α-Synuclein (total/pS129) / CSF, plasma	MSD U-PLEX; ELLA; Simoa	Unchanged in trial data ³ ; short trials unlikely to show change [#]
Neurodegeneration	Aβ40/Aβ42 ratio / CSF, plasma	Lumipulse; Simoa; MSD V-PLEX; Elecsys; ELLA	Unchanged in trial data ⁴ ; short trials unlikely to show change [#] ; include for cognitive endpoints

*literature shows upregulation of listed biomarker in PD studies, indicative of potential predictive context of use, but has not been tested in trials to date

[#]inclusion in trials is recommended, may have pharmacodynamic response in longer trials but no post-treatment changes observed in trials to date (up to 28 days)

Additional notes

- Validated clinical scales should be included in all trials to contextualize biomarker changes against functional and symptomatic outcomes. Short trials unlikely to show change, but motor improvement has been observed in an open-label PD trial⁴. Motor and non-motor scales could include: MSD-UPDRS, MDS-NMS, ACE-III for cognition, GIDS-PD, GDS-30, PDQ-39¹.
- Free IL-18 refers to the biologically active fraction not bound by IL-18BP; requires paired IL-18BP measurement and pre-specified calculation method³⁻⁴ (to provide rough estimate); ratio of IL-18BP to total IL-18 may also be meaningful rather than indirect estimated calculation.
- Simoa or ELLA preferred for low-abundance analytes; MSD U-PLEX/S-PLEX or ELLA provides advantage of multiplexing to reduce sample volume; standardized platforms ideal where possible for standardization (e.g., Cobas). All assays should be performed in CLIA-certified or equivalent lab with pre-defined QC criteria.
- Of note: cytokine measures in biofluids are particularly susceptible to diurnal fluctuations and transient activation. As such, care should be taken to draw samples at similar times of day and note any potential factors that may alter cytokine levels (e.g. recent infections) at time of draw if possible.
- Assays in development (no clinical trial data, initial validation data expected H2 2026):
 - Academic: ASC specks
 - NULISA: oligomeric ASC/NLRP3, caspase-1 (p20), GSDMD (NTD), mature IL-1β
 - Proteina: ASC specks, oligomeric ASC/NLRP3, soluble ASC/NLRP3, ASC-NLRP3 complex, caspase-1 (p20), GSDMD (NTD)
 - Simoa: total NLRP3
- Limited/conflicting markers with null or mixed results to date (recommend as exploratory markers only, if included): CXCL1, IFN-γ, IL-10, TNF-α, CSF hsCRP, plasma CCL2, plasma IL-8.^{1,3,7-8,14-15}

References

- A trial to test the use of Dapansutrile, an anti-inflammatory medication, in people with Parkinson's disease (DAPA-PD): <https://clinicaltrials.gov/study/NCT07157735>
- Proof-of-principle study of inflammasome signaling proteins as diagnostic biomarkers of the inflammatory response in Parkinson's disease: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10305113/>



3. Anti-neuroinflammatory and anti-inflammatory effects of the NLRP3 Inhibitor NT-0796 in subjects with Parkinson's disease: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12553988/>
4. Ventyx Biosciences announces positive top-line data from its Phase 2a safety and biomarker trial evaluating VTX3232 in patients with early-stage Parkinson's disease: <https://ir.ventyxbio.com/news-releases/news-release-details/ventyx-biosciences-announces-positive-top-line-data-its-phase-2a>
5. NLRP3 inhibitor passes muster in early Parkinson's trial: <https://www.alzforum.org/news/conference-coverage/nlrp3-inhibitor-passes-muster-early-parkinsons-trial>
6. IL-1B and Neurodegenerative diseases: <https://biospective.com/resources/il1beta-neurodegenerative-diseases>
7. Cerebrospinal fluid biomarkers of NLRP3 pathway, immune dysregulation, and neurodegeneration in Parkinson's disease: a meta-analysis: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12951271/>
8. Aberrations in Peripheral Inflammatory Cytokine Levels in Parkinson Disease: <https://jamanetwork.com/journals/jamaneurology/fullarticle/2553835>
9. Cerebrospinal fluid concentrations of inflammatory markers in Parkinson's disease and atypical parkinsonian disorders: <https://pubmed.ncbi.nlm.nih.gov/30185816/>
10. Interleukin-1 β , interleukin-1 receptor antagonist, interleukin-6, interleukin-10, and tumor necrosis factor- α levels in CSF and serum in relation to the clinical diversity of Parkinson's disease: <https://pubmed.ncbi.nlm.nih.gov/29478949/>
11. Parkinson's disease peripheral immune biomarker profile: a multicentre, cross-sectional and longitudinal study: <https://link.springer.com/article/10.1186/s12974-022-02481-3>
12. CSF YKL-40 level predicts the cognitive progress of de novo Parkinson's disease: <https://www.neurology.org/doi/10.1212/WNL.00000000000211680>
13. Neuroinflammation-mediated YKL-40 correlates with tau pathology and predicts longitudinal cognitive impairment and brain atrophy in Alzheimer's disease, with hypertensive dependency: <https://doi.org/10.3389/fnagi.2025.1630022>
14. Interferon- γ Involvement in the Neuroinflammation Associated with Parkinson's Disease and L-DOPA-Induced Dyskinesia: <https://pubmed.ncbi.nlm.nih.gov/33687725/>
15. Selected serum cytokines and nitric oxide as potential multi-marker biosignature panels for Parkinson disease of varying durations: a case-control study: <https://pubmed.ncbi.nlm.nih.gov/30954070/>

This document was prepared by the Michael J. Fox Foundation for Parkinson's Research. It is intended for use by clinical trial sponsors and investigators to guide, rather than dictate, biomarker selection and reflects the current state of evidence as of August 2026. Recommendations will be updated as new data emerge. For questions, contact the MJFF Biomarker Team at biomarkers@michaelfox.org.

