Scientific Rationale: Vascular Dysfunction in PD

Emerging research highlights vascular dysfunction as a potential contributor to PD pathogenesis. Post-mortem analyses have identified reduced capillary density and cerebral blood flow in the substantia nigra of PD patients (Guan et al., 2013), suggesting that chronic hypoperfusion may exacerbate neuronal stress and degeneration. FGF-1, a 16-kDa protein known for its angiogenic properties, binds to fibroblast growth factor receptors (FGFRs) on endothelial cells, activating pathways such as PI3K/Akt and MAPK to stimulate new blood vessel formation (Beenken & Mohammadi, 2009). By enhancing cerebral perfusion, FGF-1 may mitigate hypoxia, facilitate toxin clearance, and support neuronal survival, offering a novel approach to PD treatment.

Preclinical Studies: Animal Models

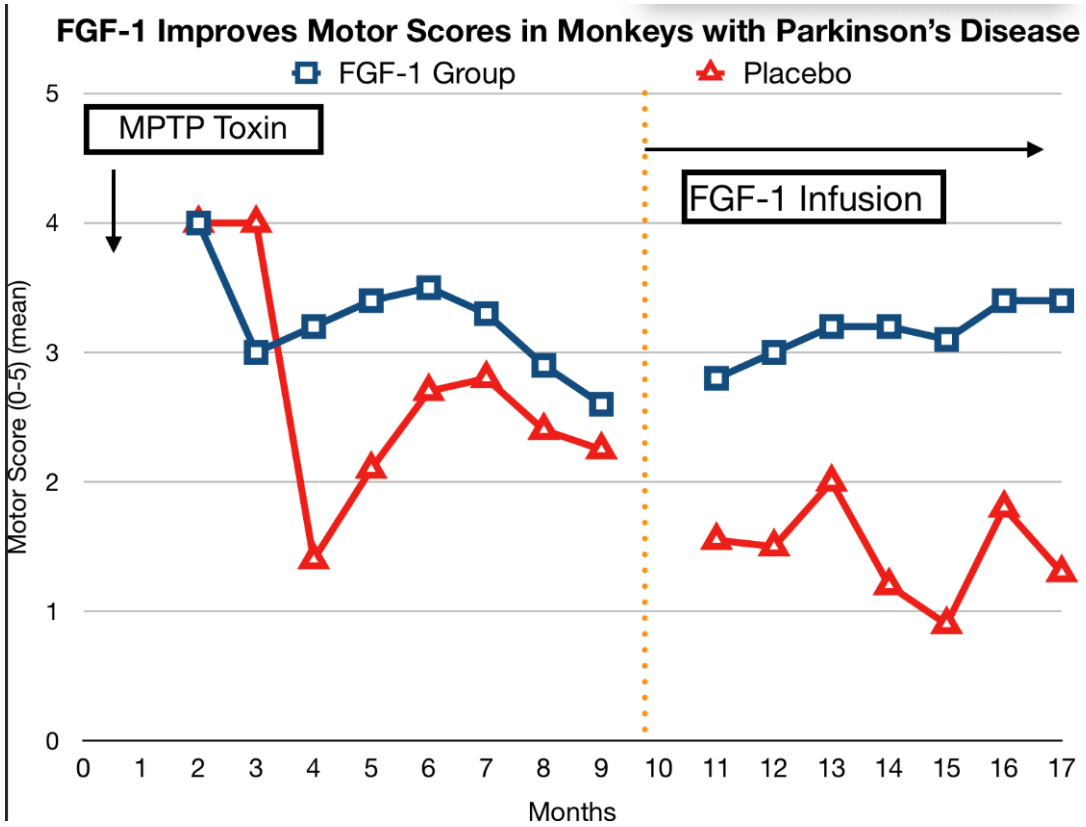
Cynomolgus Monkey Model

To assess FGF-1's therapeutic potential in PD, preclinical studies were conducted using Cynomolgus monkeys (Macaca fascicularis), a model selected for its neuroanatomical similarity to humans (Porras et al., 2012). Parkinsonism was induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that selectively targets dopaminergic neurons (Blesa et al., 2012).

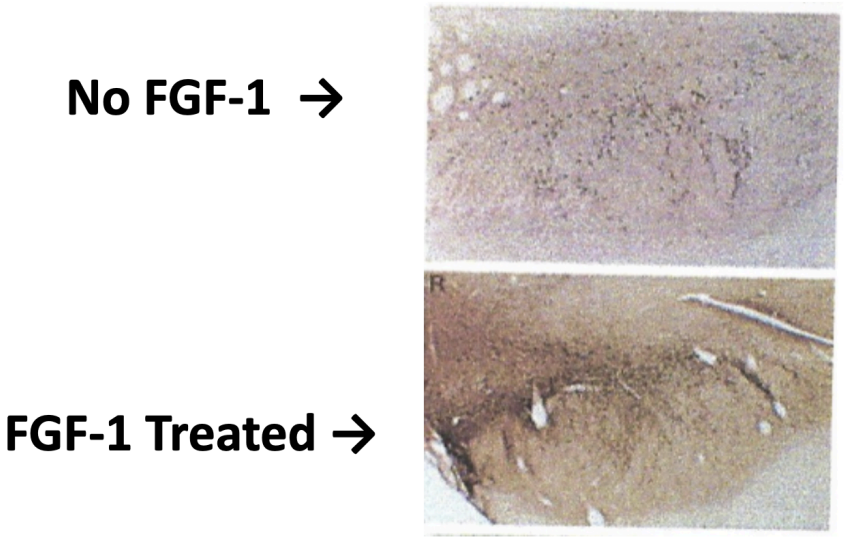
Study Design: Following MPTP administration, monkeys were randomized into two groups:

- *FGF-1-treated group:* Received FGF-1 (dose optimized from prior studies).
- *Placebo group:* Received saline.
  Motor function was assessed monthly using a standardized scale (0–5, with 5 indicating normal function), and brains were analyzed post-mortem for dopamine levels and alpha-synuclein pathology.

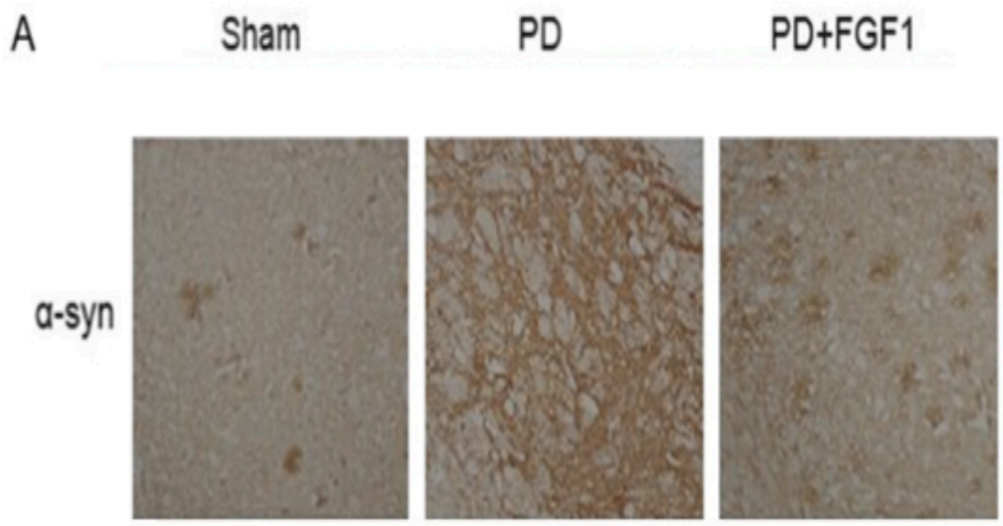
Results:

- *Motor Function:* Baseline scores averaged ~4. Post-MPTP, scores declined to ~1.5. In the FGF-1 group, treatment began at Month 9, with scores improving to ~4 by Month 17, while the placebo group showed no recovery.
    - 

- *Dopamine Levels:* High-performance liquid chromatography (HPLC) indicated a 60% increase in dopamine in the substantia nigra of treated monkeys compared to placebo.



- *Alpha-Synuclein:* A ~70% reduction in alpha-synuclein aggregates was observed in the FGF-1 group.



These findings suggest FGF-1 can reverse motor deficits, enhance dopamine production, and reduce pathological protein accumulation in a primate model.

Mouse Studies at the University of Minnesota

Separate from the McGill study, the University of Minnesota conducted safety and efficacy assessments of FGF-1 in mouse models. These studies focused on tolerability and angiogenic effects, reporting no adverse events over extended treatment periods (unpublished data). They provide additional evidence of FGF-1's safety but are not directly linked to the PD-specific primate research.

Human Studies: Safety and Efficacy

Medical Research Studies in the British Virgin Islands

Human investigations began with medical research studies in the British Virgin Islands, involving over 200 PD patients across various disease stages.

Study Design: Patients received intranasal FGF-1 twice daily for 5 days, with follow-ups at 3, 6, 12, 18, and 24 months. Motor function was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (0–108, higher scores indicating greater impairment).

Results:

- *Motor Improvement:* At 6 months, UPDRS motor scores decreased by an average of 53% (e.g., from 40 to 19), exceeding typical levodopa effects (Poewe et al., 2017).
- *Safety:* No serious adverse events were reported; mild nasal irritation and headaches were the primary side effects.

These outcomes indicate FGF-1's potential to improve motor function and its tolerability in a clinical population. Please note that these studies were done in medical research studies, not as US FDA studies.

Empirical Evidence: fMRI Data from Washington University

In 2024, we partnered with Washington University in St. Louis, a leader in neuroimaging, to validate these clinical outcomes with objective data. This study uses fMRI to measure cerebral blood flow in PD patients pre- and post-FGF-1 treatment.

Study Design

- *Participants:* Patients with moderate-to-advanced PD
- *Protocol:* Baseline fMRI scans were followed by intranasal FGF-1 (twice daily, 5 days), with post-treatment scans at 6 months.
- *Focus:* Blood flow to the substantia nigra, assessed via arterial spin labeling (ASL) fMRI.

Key Findings

- *21% Blood Flow Increase:* In January 2025, the first patient's post-treatment fMRI revealed a 21% increase in substantia nigra blood flow. This correlated with a 50% UPDRS improvement, linking perfusion gains to clinical outcomes.
- *Ongoing Research:* Data collection continues, with preliminary trends suggesting consistent increases across additional patients (results pending).

This finding may be historic—the first documented therapeutic enhancement of cerebral blood flow in PD—supporting our angiogenesis hypothesis and aligning with preclinical vascular improvements.

US FDA Phase IIA Trial for Coronary Artery Disease at the University of Cincinnati

FGF-1's safety profile was further evaluated in a US FDA-approved Phase IIA trial at the University of Cincinnati for coronary artery disease (CAD), a condition also characterized by vascular insufficiency.

Study Design: Patients with CAD received intracoronary FGF-1 to stimulate angiogenesis and improve cardiac perfusion. Outcomes included exercise tolerance and angina symptoms, with safety monitored via adverse event reporting.

Results:

- *Efficacy:* All patients exhibited improved exercise capacity and reduced angina.
- *Safety:* No adverse events attributable to FGF-1 were observed.

Published in Circulation, the American Heart Association's journal, this study demonstrated FGF-1's safety and angiogenic efficacy in humans (Schumacher et al., 1998). Two additional trials in Germany, collectively treating over 80 CAD patients with FGF-1, reported similar improvements without serious adverse events, reinforcing its safety across populations.

Conclusion and Future Directions

Zhittya Genesis Medicine's research on FGF-1 for PD has progressed from preclinical studies—demonstrating motor recovery, dopamine restoration, and alpha-synuclein reduction in Cynomolgus monkeys—to human studies showing a 53% improvement in UPDRS motor scores and a consistent safety profile across over 200 PD and 80 CAD patients. The US FDA Phase IIA trial for CAD, and additional trials in Germany, such as those published in *Circulation* (Schumacher et al., 1998) further validate FGF-1's safety and therapeutic potential. Future efforts will focus on US FDA-approved randomized controlled trials to rigorously confirm these findings.

We welcome questions or discussion with neurologists interested in this research. For further information, please contact me at 702-758-9866 or sergiy@zhittyamedicine.com.

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