Updates in Therapeutics for Parkinson's Disease

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Disclaimer

- I was involved in the adaptive DBS study at Stanford, but other than that I am not involved in any of the ongoing trials discussed today. I don't formally endorse any of the trials or treatments discussed today.
- The goal of this talk is to educate you on the latest therapeutics for PD

Types of treatments

Disease Modifying Therapies

- **Slow** or **halt** the progression of neuron dysfunction / neuron death (*i.e.* therapies that prevent further neurons from being impacted by the disease)

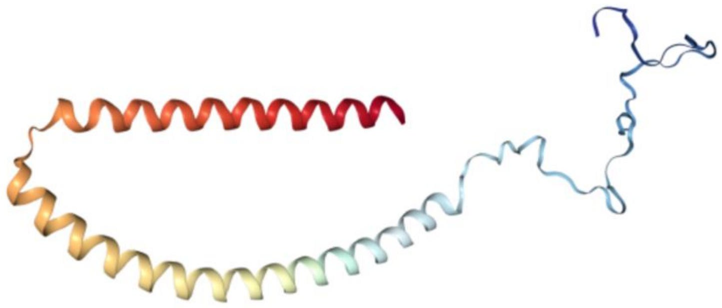
Symptomatic Therapies

- **Improve** / **restore function** for the patient (*i.e.* therapies that improve motor function, cognitive function, etc)

Disease Modifying Approaches

- α-synuclein reduction
- LRRK2 inhibition
- Neuroinflammation reduction
- Blocking c-Abl kinase
- Gene Therapy

Targeting α-synuclein



Hypothesis:

- Various triggers cause the α-synuclein protein to misfold
- This misfolded protein propagates throughout the brain causing neuron dysfunction and neuron death resulting in PD

Goal:

- Stop α-synuclein misfolding and/or propagation

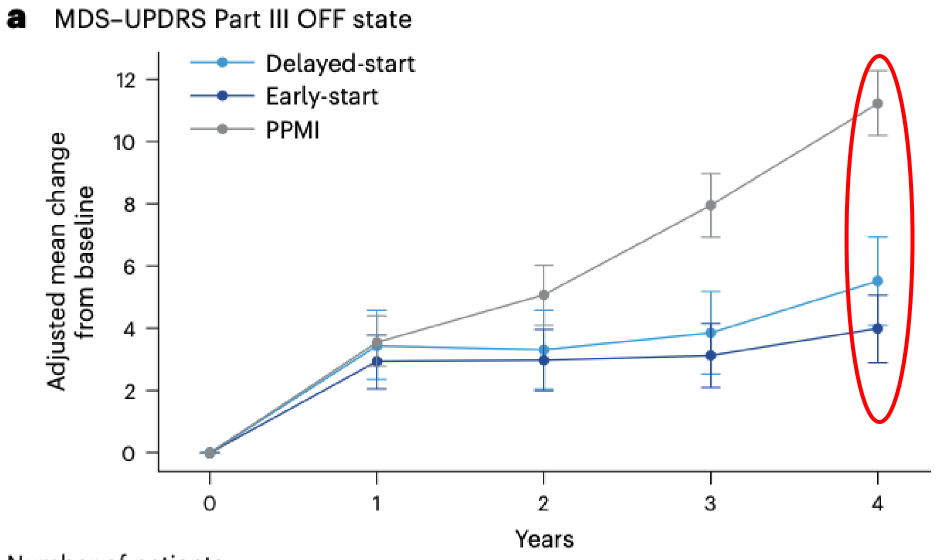
Strategies:

- Passively provide antibodies against α-synuclein
- Have the body generates its own antibodies to α-synuclein (i.e. an α-synuclein vaccine)
- Have a small molecule interfere with α-synuclein
- Create a protein that breaks misfolded α-synuclein

Targeting α-synuclein

Prasinezumab

- Antibody against α-synuclein
- Phase 2 PASADENA trial in early Parkinson's disease (could not be on dopamine medications at start of trial) was overall negative (2022)
- However, possibly a positive signal on the digital/wearable markers
- Additionally, on analysis of open label extension data there was a positive signal when comparing the data to a 'real world group' (over 3-4 year period)
- A Phase 2b PADOVA trial in early Parkinson's disease (but you *could* be on dopamine medications at the start of the trial) completed, showing positive signals
  - Trend towards slower progression overall, and in a pre-specified subgroup of patients on stable LDOPA treatment, it was statistically significant
- **Therefore, a Phase 3 trial for Prasinezumab will proceed**
  - We hope to have this trial at Stanford



Number of patients

	0	1	2	3	4
Delayed-start	94	93	83	83	75
Early-start	177	175	149	147	143
PPMI	303	215	185	182	180

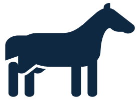
nature medicine

Article https://doi.org/10.1038/s41591-024-03270-6

Sustained effect of prasinezumab on Parkinson's disease motor progression in the open-label extension of the PASADENA trial

Targeting α-synuclein

ABL301



- Antibody against α-synuclein that goes into brain better (‘Trojan-Horse’ mechanism)
- Phase 1 study completed showing it was safe and well tolerated
- Planning for Phase 2
- Video showing how treatment works:
  - https://www.youtube.com/watch?v=nM3X_U11VuY

ACI-7104

- **Vaccine** against α-synuclein
- Stimulates immune system to generate its own antibodies against α-synuclein
- Phase 2 *VacSyn* trial had positive interim data, with signs of clear antibody formation, well-tolerated without safety issues
- We are awaiting more results

Ambroxol

Glucocerebrosidase is a protein that helps brain cells clean up ‘waste’ they no longer need

Mutations in Glucocerebrosidase are associated with an increased risk in Parkinson’s disease

Ambroxol appears to increase Glucocerebrosidase activity in brain cells, allowing cells to clean up ‘waste’ better which may protect the brain cells

It was tested in a Phase 2a trial in 17 PD patients in 2020

- It was safe and they showed it was able to get into the brain and act on Glucocerebrosidase their target

Ambroxol is used in cough syrup in some countries as it helps break up phlegm.

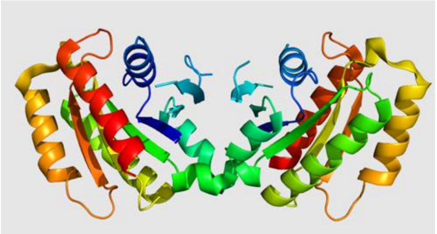
It is NOT approved in the United States.

In PD trials, a very high dose of Ambroxol was used. Please do not take Ambroxol on your own.

Ambroxol – What's Next

- A Phase 3 study (ASPro-PD) has started in the UK
- 330 patients total
  - Some patients will take Ambroxol and some will take placebo, for 2 years
  - Their quality of life and movement ability will be compared at the 2-year mark

LRRK2 Inhibitors



Hypothesis:

- Certain mutations in the gene LRRK2 contribute to the development of PD
- The enzyme encoded by the mutated gene is hyperactive
- This LRRK2 enzyme hyperactivity leads to PD (exactly how is unclear)

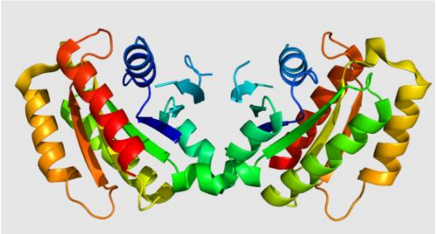
Goal:

- Design a way to slow down the LRRK2 enzyme

Strategies:

- Small molecules
- Genetic modifications

LRRK2 Inhibitors



BIIB122 - Small molecule LRRK2 inhibitor

- Phase 2b study is underway
- Both in patients with and without LRRK2 mutations
- Still enrolling at UCSF for those that have confirmed LRRK2 mutations: https://clinicaltrials.ucsf.edu/trial/NCT06602193

NEU-411 - Small molecule LRRK2 inhibitor

- It is recruiting individuals with what the company terms "LRRK2-driven Parkinson's". This is based on a saliva biomarker test showing evidence of LRRK2 pathway overactivity.
- Trial is in process / starting up:
  - https://clinicaltrials.gov/study/NCT06680830

BHV-8000 - Targeting Neuroinflammation

What is it?

- An oral medication designed to slow or stop Parkinson's progression by **reducing chronic inflammation in the brain**. It works by inhibiting two proteins, TYK2 and JAK1, which are involved in regulating the immune system's response.
- In Phase 1 clinical testing of 58 healthy adults, BHV-8000 was found safe and well tolerated when given as single or multiple daily oral doses.
  - BHV-8000 entered the brain and maintained levels high enough to inhibit at least half of TYK2 and JAK1 activity.
  - Compared with a placebo, it also led to significant reductions in blood biomarkers of inflammation.

Clinical Trial Status:

- **Currently in a Phase 2/3 clinical trial to evaluate its effectiveness and safety.**
  - **Population:** Recruiting up to 550 individuals (ages 40-85) with early-stage idiopathic Parkinson's disease (diagnosed within the last 2 years).
  - **Design:** Patients will receive a daily dose of 10mg or 20mg of BHV-8000 or a placebo for up to 48 weeks.
  - **Primary Goal:** To determine if the therapy can slow functional decline
  - We may have this trial at Stanford, TBD

VENT-02 - Targeting Neuroinflammation

What is it?

- An oral medication that inhibits the NLRP3 inflammasome. The NLRP3 inflammasome is a protein complex that drives an inflammatory response in the brain.

The Goal:

- **To reduce chronic brain inflammation, with the potential to provide both symptom relief and slow disease progression.**

Clinical Trial Status:

- A Phase 2a clinical trial has dosed its first patient and is actively enrolling participants with mild to moderate Parkinson's disease.

Trial Details:

- The study aims to enroll about 30 people to assess the treatment's safety, tolerability, and preliminary effectiveness.
- It will use digital health technologies and a comprehensive set of biomarkers to measure the drug's effect on symptoms and inflammation.
- Top-line data from the current study are expected by the end of 2025 or early 2026.

Risvodeninib – Targeting c-Abl Kinase

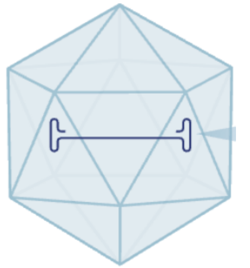
What is it?

- An oral capsule designed to slow or stop Parkinson's progression. It works by blocking an overactive enzyme called c-Abl kinase, which is believed to contribute to the disease. **The goal is to protect the brain's dopamine-producing nerve cells from damage.**

Clinical Trial Status:

- A 12-week Phase 2 study has been completed, and the design for a Phase 3 study is being planned with FDA input.
- **Phase 2 Results:** The study found that patients treated with risvodetinib had improvements in both the severity of their symptoms (measured by MDS-UPDRS) and their ability to perform daily activities when compared to a placebo.

AAV-GDNF Gene Therapy



What is it?

- A gene therapy (AB-1005) that uses a harmless adeno-associated virus (AAV2) to deliver the gene for a **protective "growth factor"** (GDNF) directly to the brain. **The goal is to protect and restore dopamine neurons.**
- This type of approach has had negative results in the past

Clinical Status:

- A Phase 1b study showed a favorable safety profile over 36 months and positive trends on clinical outcomes.
- Based on these results, the FDA granted it a Regenerative Medicine Advanced Therapy (RMAT) designation in February 2025 to help accelerate its development.
- A larger Phase 2 trial, REGENERATE-PD, is now enrolling patients.

The REGENERATE-PD Phase 2 Trial:

- This is a randomized, double-blind, sham surgery-controlled study.
- It is enrolling approximately 87 patients with moderate-stage Parkinson's disease.
- The trial's main goal is to measure changes in motor function over 18 months after the procedure.
- **Recruiting at UCSF:**
  - https://clinicaltrials.ucsf.edu/trial/NCT06285643

Updates on Drugs from last talk:

- The GLP-1 drug, **Exenatide**, unfortunately did not show benefit over placebo in PD in a large Phase 3 trial. There may be a few ongoing GLP-1 trials in Phase 2, but unfortunately overall I suspect it is unlikely this class will be helpful in slowing down PD.

- **Buntanetap** finished its Phase 3 trial. Exact situation is unclear. It did show positive signals in some secondary and subgroup endpoints. However, from what I am inferring, it likely did not meet its primary goal
  - (not confirmed, sources on this vary, see: https://www.parkinson.org/blog/awareness/new-parkinsons-medications)

Symptomatic Therapies

- Tavapdon
- Solengepras
- CPL'36 (for dyskinesias)
- Subcutaneous infusions
- Focused ultrasound
- Stem cells
- DBS

Tavapadon

What is it?

- Once-daily oral pill that works in a unique way against certain dopamine receptors (D1/D5)

The Goal:

- The mechanism is designed to **improve motor symptoms while potentially avoiding side effects associated with other dopamine agonists**, like impulse control disorders and somnolence.

Clinical Trial Results:

- The entire Phase 3 TEMPO clinical trial program reported positive results.
- **In early PD**, it showed a statistically significant and clinically meaningful improvement on scores for motor experiences of daily living and motor examination compared to placebo.
- **In advanced PD**, as an add-on to levodopa, it significantly increased daily "ON" time without troublesome dyskinesia by 1.1 hours more than placebo.

Status & Next Steps:

- Based on this data, **AbbVie submitted a New Drug Application to the FDA in September 2025.**
- A decision is hoped for in 2026.

Solengepras

What is it?

- An oral therapy with a novel, non-dopaminergic mechanism.

The Goal:

- It aims to rebalance brain motor circuits by targeting the GPR6 receptor, **improving motor function without directly manipulating dopamine levels or receptors**. This may help manage functional impairments and non-motor symptoms with less side effects than current treatments.

Clinical Trial Results (A Mixed Profile):

- **Positive as an Add-on Therapy:** A Phase 2 trial in patients already taking levodopa was successful, meeting its goal of significantly reducing daily "OFF" time.
- **Missed Goal as a Standalone Therapy:** The more recent Phase 2 ASCEND trial in early, untreated PD did not meet its primary endpoint for improving motor symptoms. However, it showed encouraging trends on patient-reported measures of daily function and non-motor symptoms like sleepiness.

Status & Next Steps:

- A pivotal Phase 3 trial called ARISE is now underway, evaluating solengepras as an adjunctive therapy in patients with motor fluctuations. Topline data are expected in the first half of 2026.

CPL’36: A New Oral Therapy for **Dyskinesia**

What is it?

- CPL’36 is an oral small molecule designed to ease levodopa-induced dyskinesia (LID), the uncontrolled movements that can be a side effect of levodopa treatment.

Mechanism:

- It works by inhibiting the PDE10A enzyme in the brain's striatum. This is intended to normalize nerve signaling and improve motor function.

Clinical Trial Status:

- A Phase 2 study testing CPL’36 against a placebo in 105 adults with Parkinson's and LID is complete.
- **Phase 2** Results (Positive):
  - **The study met its main goal, showing a clinically meaningful and statistically significant reduction in dyskinesia.**
  - After four weeks, patients on the 20mg and 40mg doses improved by 12.3 and 13.6 points, respectively, on the Unified Dyskinesia Rating Scale (UDysRS) compared to placebo.
  - Improvements in motor symptoms were seen as early as one week after starting treatment.
- Safety:
  - The most common side effect was mild to moderate drowsiness. Severe side effects were reported less frequently in the CPL'36 groups than in the placebo group.

Subcutaneous Infusions (FDA approved)

Vyalev (foslevodopa-foscarbidopa)

Phase 3 trial showing improvement in ON time without troublesome dyskinesias

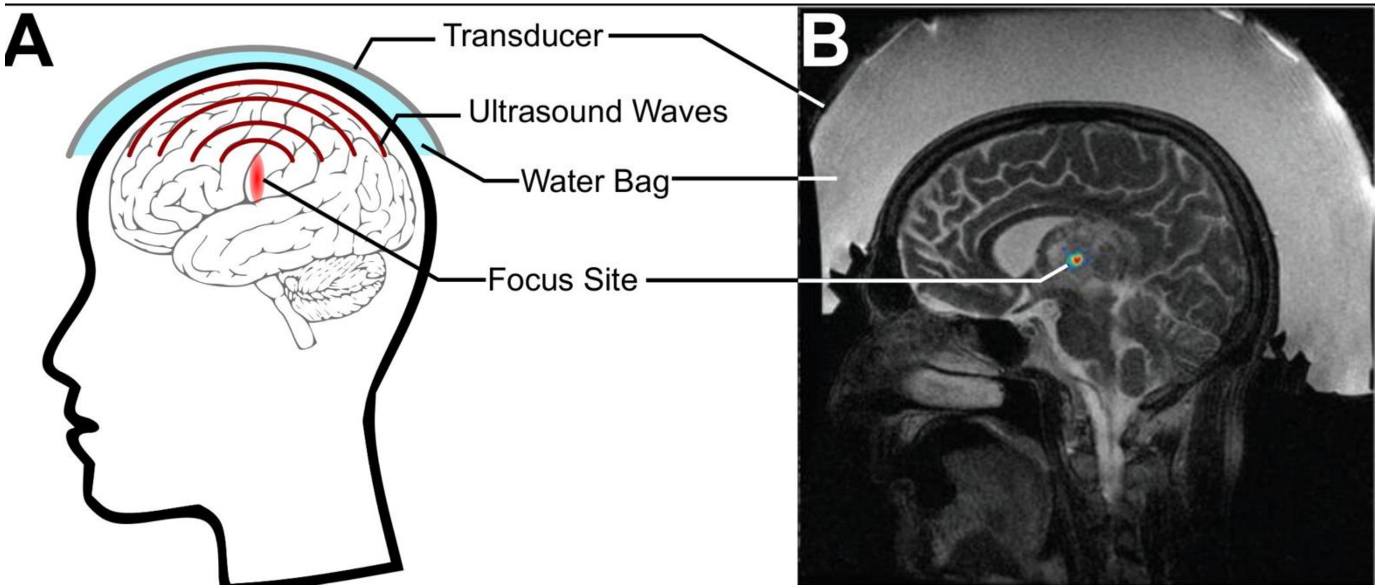
Onapgo (apomorphine)

Phase 3 trial showing reduced "off" time and increased "on" time for patients experiencing motor fluctuations

Focused Ultrasound

Focused non-ionizing ultrasonic waves to lesion tissue

- Targets in the brain:
  - Thalamus (for tremor only)
  - Globus Pallidus (primarily for dyskinesias)
  - Subthalamic Nucleus
  - **Pallidothalamic tract (new)**



Stem Cells for PD

Unfortunately, symptomatic only

- *Not* being used as a cure
- Replaces dopamine, does not prevent spread of disease

Logic:

- Dopamine cells are dying, let's replace them

Trials done in 1980s and 1990s with mixed effects

- Some benefited, some had no effect, and some worsened due to uncontrollable dyskinesias

Trying again with argument that we have better quality stem cells and surgical techniques

Stem Cells for PD

Bemdaneprocel

- An "off-the-shelf" (allogeneic) therapy using dopaminergic neuron precursors derived from a human embryonic stem cell line.
- **Phase 3 trial (exPDite-2) has begun**, with the first patient treated in September 2025.
- **Phase 1 Results:**
  - The therapy was demonstrated to be safe and well-tolerated
  - PET imaging confirmed transplanted cells survived in the brain.
  - Patients in the high-dose group gained an average of **2.7 hours of "ON" time** per day
- **Phase 3 Trial Design:**
  - A large, multi-center, randomized, double-blind, sham surgery-controlled study that will enroll approximately 102 participants.
  - Hope to have this at Stanford

ANPD001

- A personalized (autologous) therapy that uses a patient's *own* skin cells to create new dopamine neuron precursors for transplantation.
- Because it uses the patient's own cells, immunosuppressant drugs are not needed, which is expected to reduce side effects like infections.
- Currently in a **Phase 1/2a study (ASPIRO)**, with the third group of patients now receiving the treatment.

Deep Brain Stimulation (DBS) updates

Adaptive Deep Brain Stimulation (aDBS): FDA Approval

- The most significant advance in neuromodulation for PD since the initial approval of DBS is the advent of adaptive, or "closed-loop," systems. Traditional DBS delivers continuous, open-loop stimulation at a fixed setting, regardless of a patient's fluctuating symptoms or brain state. In contrast, aDBS systems can sense pathological neural activity in real-time and automatically adjust stimulation on a moment-to-moment basis.
- In early 2025, the FDA approved the Medtronic Percept™ neurostimulator with BrainSense™ technology

Expanding DBS Targets: Nucleus Basalis of Meynert (NBM) for Cognition

- Dr. Helen Bronte-Stewart at Stanford University is evaluating the safety and tolerability of a novel approach that combines traditional STN-DBS for motor symptoms with simultaneous NBM-DBS for cognitive and cognitive-motor symptoms in PD patients
- https://clinicaltrials.stanford.edu/trials/c/NCT05968703.html

Summary – New Therapeutics for PD

- **Disease Modifying Therapies**
  - α-synuclein reduction
  - LRRK2 inhibition
  - Neuroinflammation reduction
  - Blocking c-Abl kinase
  - Gene Therapy

- **Symptomatic Therapies**
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Q&A