# A TOUR OF THE CUTTING EDGE OF PARKINSON'S TREATMENTS

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- Movement Disorders Specialist
- Residency & Medical School: The Icahn School of Medicine of Mount Sinai in New York City
- Fellowship: UC San Diego
- Since 2016- Kaiser Permanente San Rafael
- Academic interests: environmental causes of Parkinson’s, lifestyle management for prevention and symptom management of neurologic disease


# TOUR MAP

1. Vaccines and immunotherapy
2. Oral drugs
3. Gene Therapy
4. Gait treatments
5. Miscellaneous

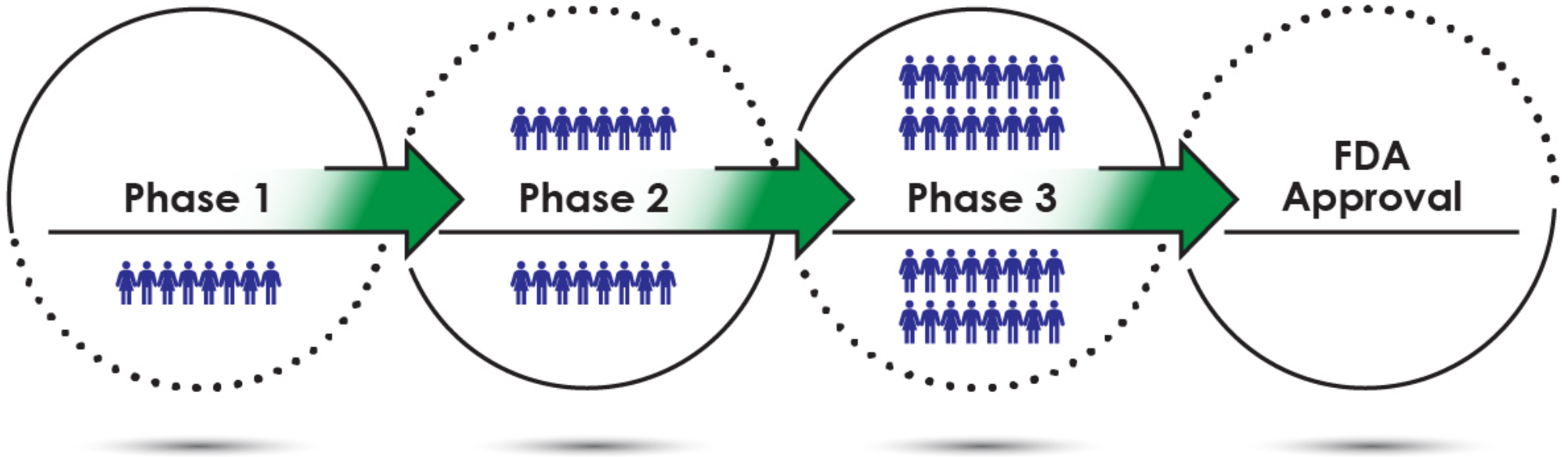
# STUDY PARTICIPATION

- Note Clinical Trial “identifier”

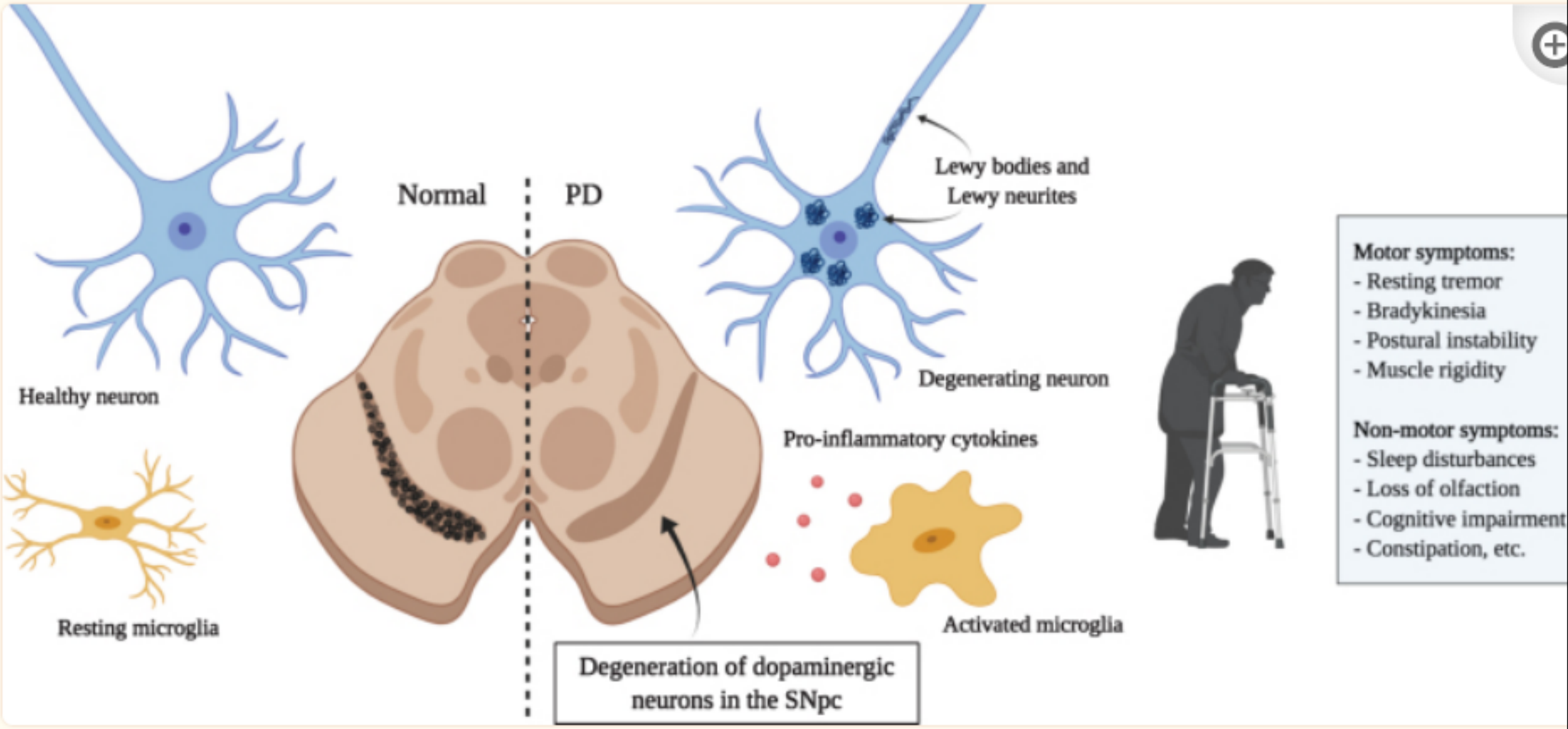
NCT Number: The National Clinical Trial number is an identification that ClinicalTrials.gov assigns a study when it is registered

- highlighted those at UCSF

# STUDY PHASES: WHAT ARE THEY?




PLACEBO


Normal
PD
Healthy neuron
Lewy bodies and
Lewy neurites
Degenerating neuron
Pro-inflammatory cytokines
Resting microglia
Activated microglia
Degeneration of dopaminergic neurons in the SNpc
Motor symptoms:
- Resting tremor
- Bradykinesia
- Postural instability
- Muscle rigidity
Non-motor symptoms:
- Sleep disturbances
- Loss of olfaction
- Cognitive impairment
- Constipation, etc.

# How Vaccines work

- Two related strategies to protect against this accumulation of alpha-synuclein

1) Introduction of antibodies to alpha-synuclein into the body, also known as *passive immunity*

2) Introduction of a molecule that induces the body to produce its own antibodies against alpha-synuclein, also known as *active immunity*

# Vaccine therapies

| | Phase | Sponsor | Outcomes | Clinical Trial Identifier |
|---|---|---|---|---|
| AFFITOPE-PD01A | 1b | Affiris | Well tolerated and safe | NCT02618941 |
| PRX002/Prazinezumab | 2 | Roche/Prothena | No motor clinical change after 52 weeks, improved 2ndary end points | NCT03100149 |
| BIIB054/Cinpanemab | 2 | Biogen | Safe, further data pending | NCT03318523 |

# CHALLENGES OF VACCINE

- Efficacy at later stages (does it need to be administered earlier)
- Avoiding autoimmune reaction
- Is alpha synuclein the only process to blame?
- Very mixed results so far, with no benefit in large studies with smaller studies pending

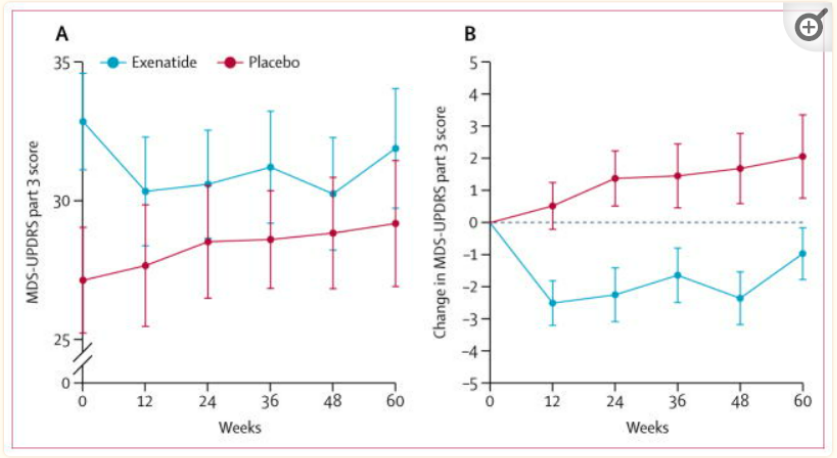



Figure 2

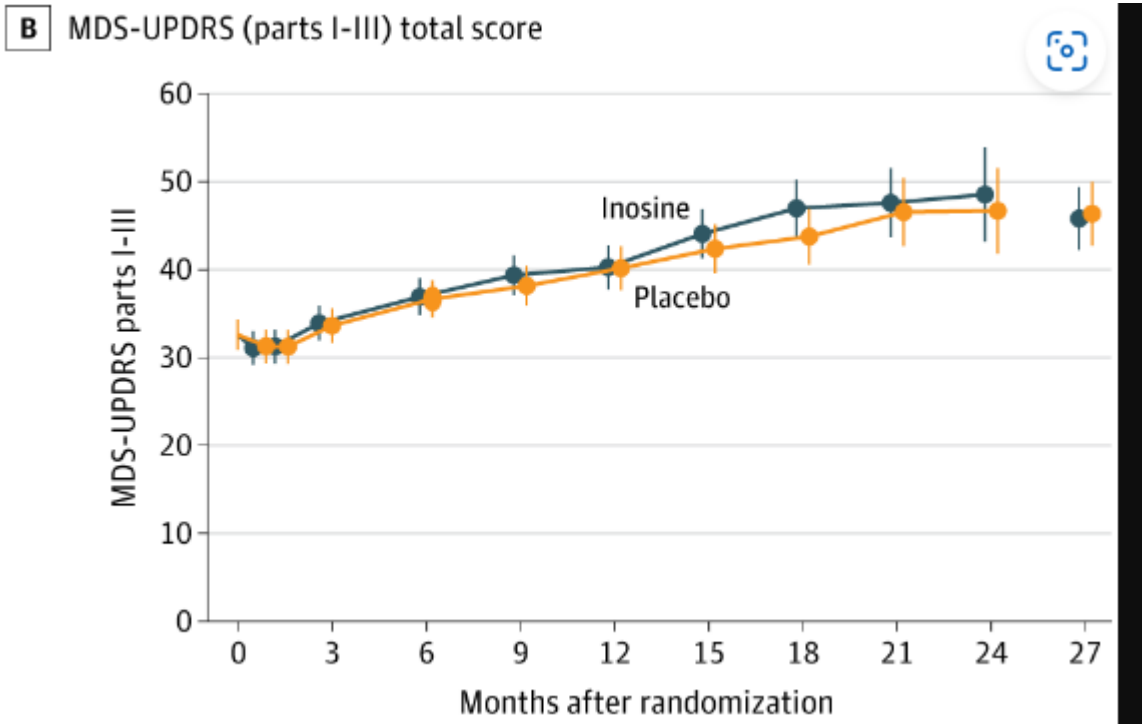
**MDS-UPDRS part 3 scores (A) and changes in MDS-UPDRS part 3 scores (B), by study visit Data are means for the off-medication state. Error bars represent standard error of the mean**

# Oral Drugs

- Exenatide
  - Crosses Blood Brain Barrier
  - Treats diabetes type 2
  - Large Phase 3 study pending

# Oral Drugs

- Inosine
  - Reduces Urate levels and inflammation
  - Large Phase 3 study ended early, negative results



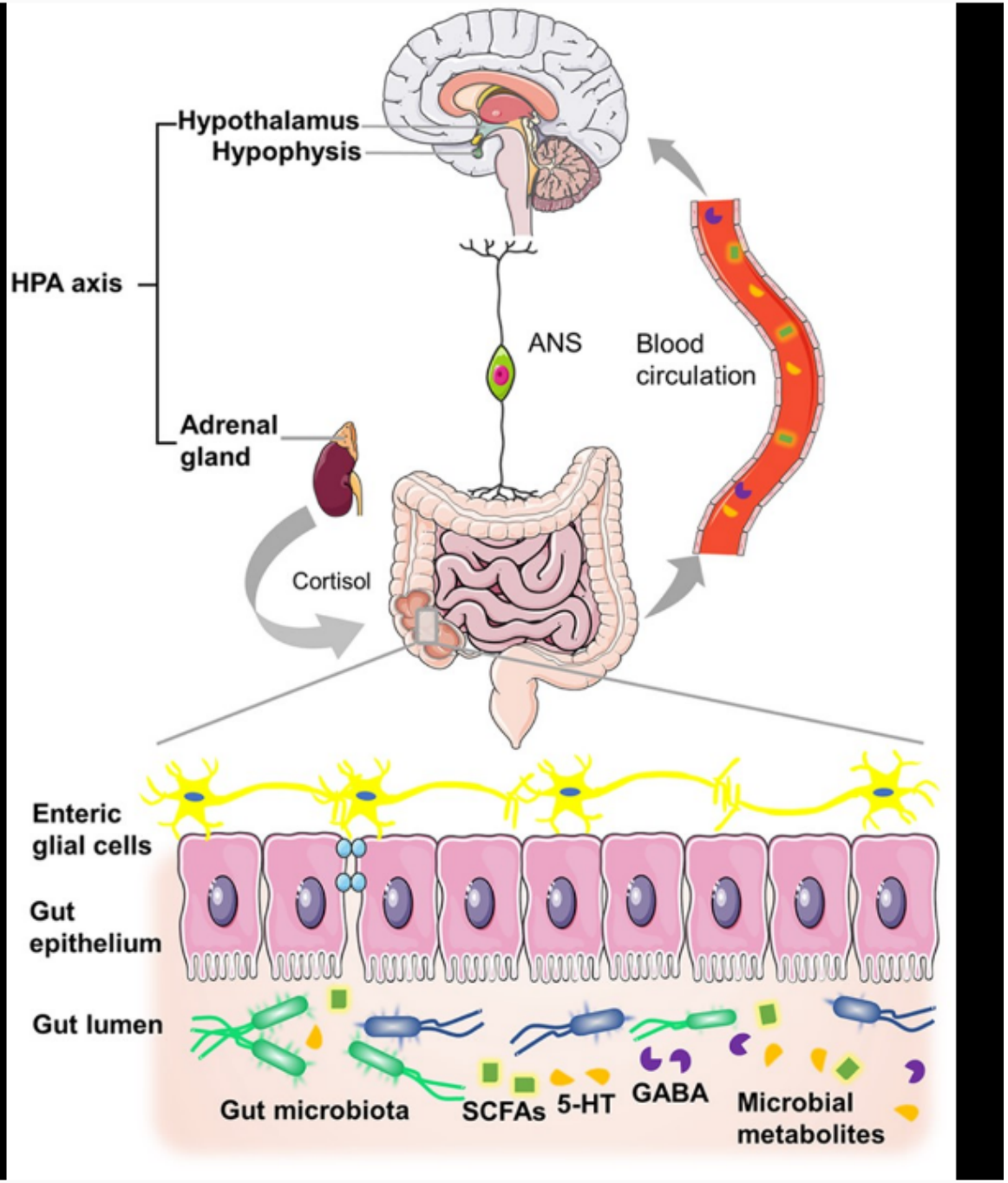
# Oral Drugs

- Deferipone
  - Reduces iron levels
  - Large Phase 3 showed worsened symptoms on patients without medication (early PD)

Table 2. Primary, Secondary, and Exploratory Clinical Outcomes (Intention-to-Treat Population).*

| Outcome | Deferiprone (N=186) | Placebo (N=186) | Mean Adjusted Difference (95% CI)† |
|---|---|---|---|
| Score on MDS-UPDRS part III | | | |
| Value at wk 36 | 31.8±14.0 | 25.9±11.7 | |
| Change from baseline (95% CI) | 9.8 (8.2 to 11.3)† | 4.0 (2.7 to 5.3)† | 5.8 (3.8 to 7.7) |
| Score on MDS-UPDRS part II | | | |
| Value at wk 36 | 10.2±7.7 | 7.1±5.4 | |
| Change from baseline (95% CI) | 4.2 (3.4 to 5.1)† | 1.8 (1.0 to 2.6)† | 2.5 (1.3 to 3.6) |
| Sum of scores on MDS-UPDRS parts II and III | | | |
| Value at wk 36 | 42.2±18.8 | 33.1±15.0 | |
| Change from baseline (95% CI) | 14.2 (12.2 to 16.1)† | 5.9 (4.1 to 7.6)† | 8.3 (5.7 to 10.8) |
| **Exploratory clinical outcome§** | | | |
| Score on MDS-UPDRS part I | | | |
| Value at wk 36 | 8.2±5.9 | 6.2±4.6 | |
| Change from baseline (95% CI) | 2.0 (1.3 to 2.7)† | 0.2 (−0.4 to 0.9)† | 1.8 (0.8 to 2.8) |

# Gut Microbiome




Changes in microbes associated with Parkinson's disease

More Longitudinal study is needed!

# Microbiota Intervention to Change the Response of Parkinson's Disease

**Status at UCSF**
accepting new patients
**Start Date**
July 2019
**Completion Date**
December 2023 (estimated)
**Sponsor**
University of California, San Francisco
**ID**
NCT03575195
**Phase**
Phase 1/2 Parkinson's Disease Research Study
**Study Type**
Interventional
**Participants**
Expecting 86 study participants

-Analysis of the microbiome in PD

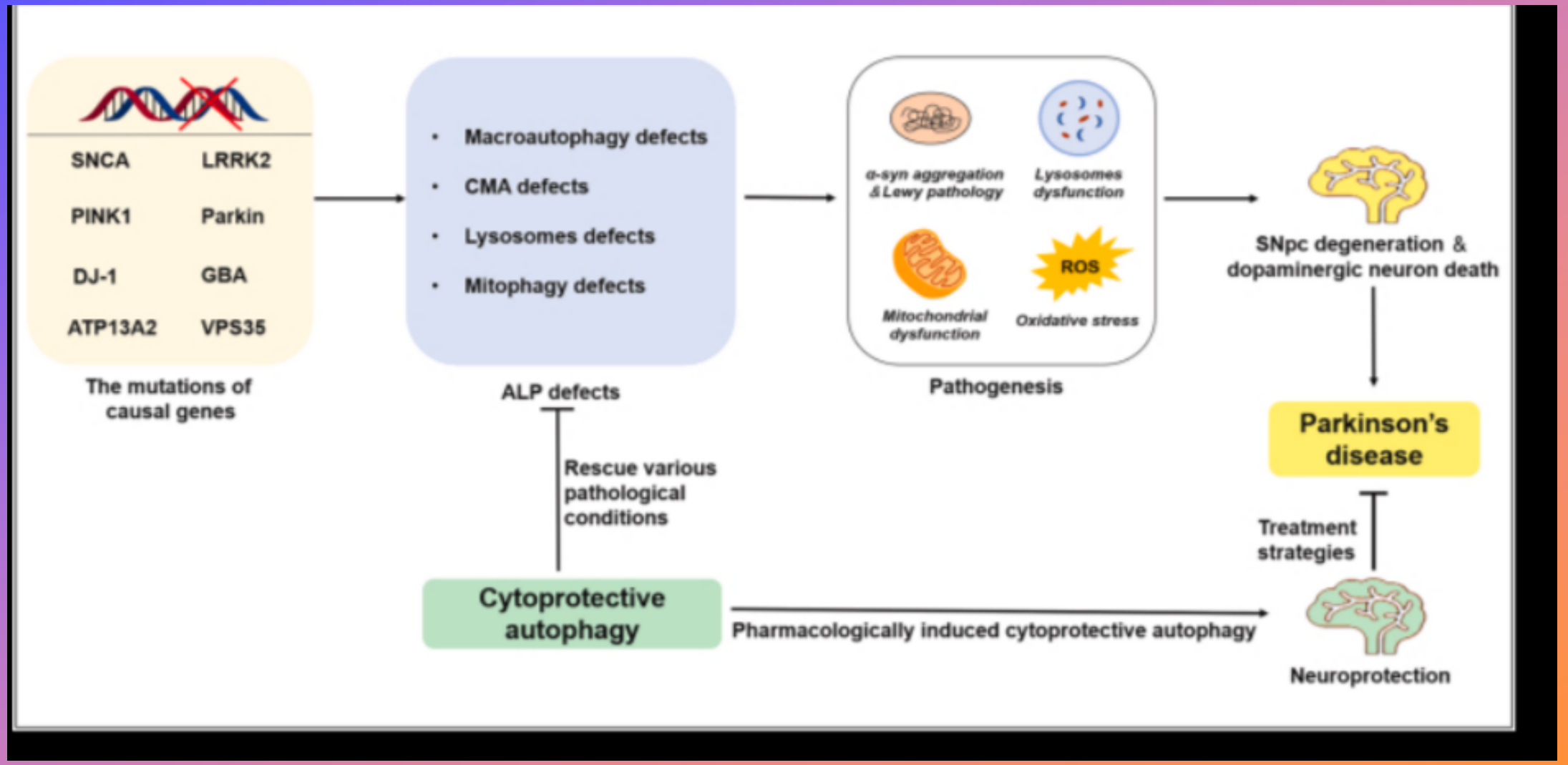
-does treatment with an antibiotic allow levodopa to work better?

UCSF Health


# Oral Probiotics

- Class I evidence for probiotics as a treatment for constipation in PD.
- The effects of probiotics on other PD aspects, such as motor disability and cognitive function, and its long-term efficacy (including effects on PD drug absorption in the gut) have not been investigated adequately.

# GENE THERAPY



# PD GENEration: Mapping the Future of Parkinson's Disease

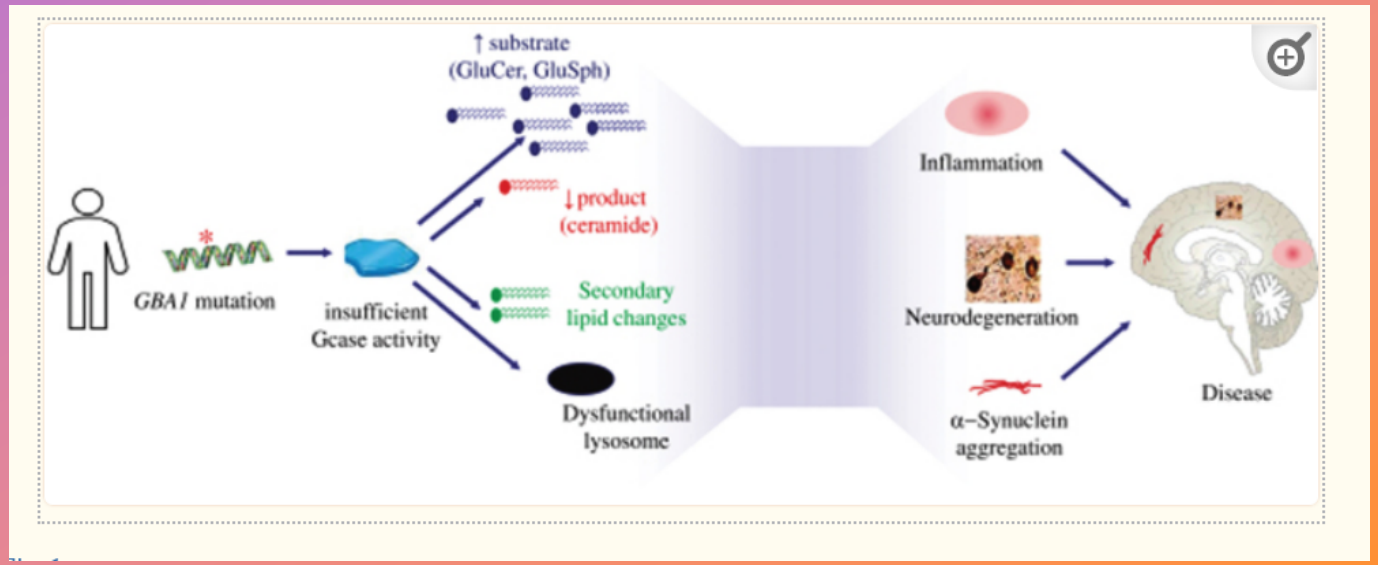
Parkinsons.org research project (currently wait list)

National initiative that offers genetic testing for clinically relevant Parkinson's-related genes and genetic counseling at no cost for people with Parkinson’s disease (PD).

# GENE THERAPY

GBA1

- Among the lysosomal genes involved, *GBA1* has the largest impact on Parkinson's disease risk. Deficiency in the *GBA1* encoded enzyme ultimately results in toxicity and inflammation and negatively affect many clinical aspects of Parkinson's disease, including disease risk, the severity of presentation, age of onset, and likelihood of progression to dementia
- Phase 1 study

# GENE THERAPY

LRRK2

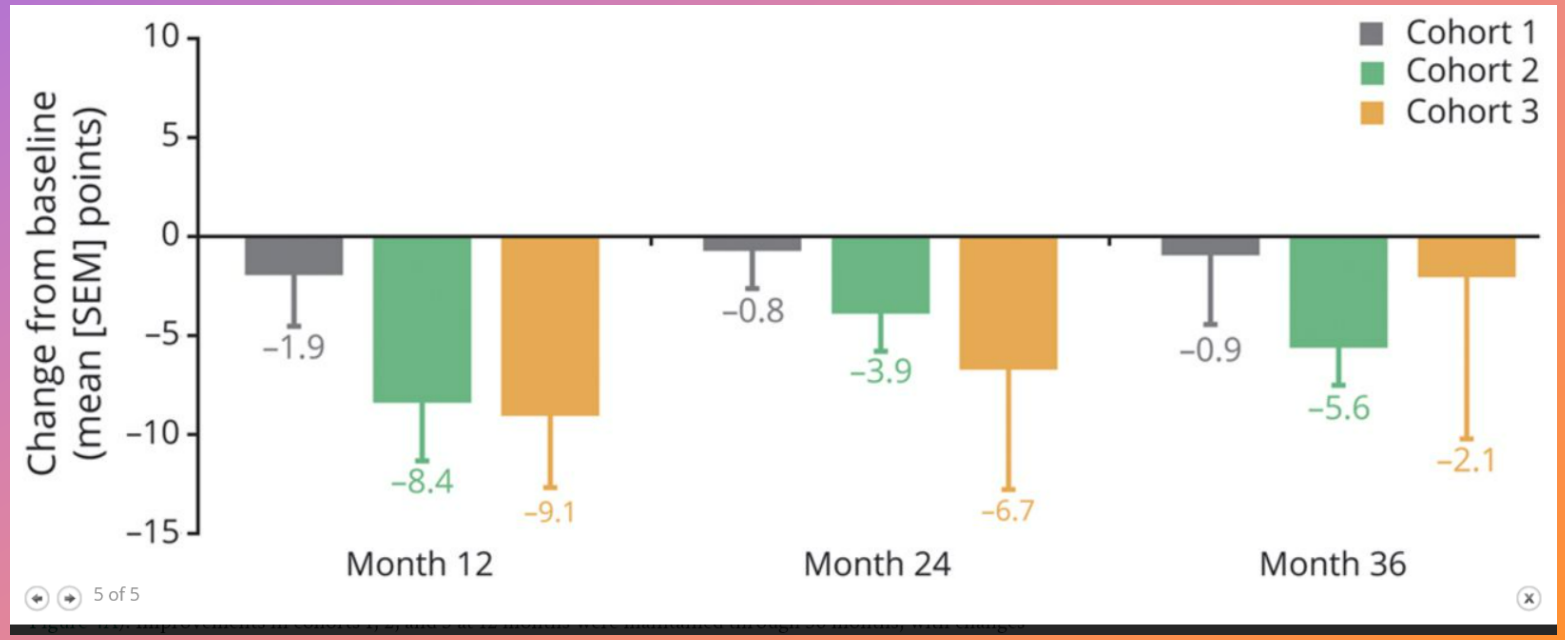
- One of the most common monogenic forms of Parkinson disease (PD) is caused by mutations in the LRRK2 gene that encodes leucine-rich repeat kinase 2 (LRRK2).
- LRRK2 mutations, and particularly the most common mutation Gly2019Ser, are observed in patients with autosomal dominant PD and in
- LRRK2 kinase inhibitors can be neuroprotective in preclinical models of PD
- BIIB122
- Phase 3 study UCSF and nationally: ClinicalTrials.gov Identifier: NCT05418673

# GENE THERAPY

## VY-AADC01

- VY-AADC01, an experimental AAV2 gene therapy encoding the human aromatic L-amino acid decarboxylase (AADC) enzyme designed to increase dopamine production from medication
- VY-AADC01 was delivered via bilateral, intraoperative MRI-guided putaminal infusions
- Phase 3 study UCSF and nationally
  - ClinicalTrials.gov Identifier: NCT05418673

UCSF Health



# INFUSIONS

## Subcutaneous infusions of levodopa

| | | |
|---|---|---|
| ND0612 | Continuous subcutaneous levodopa/carbidopa pump | Phase 2 trials ($n$ = 68) showed a reduction of approximately 2 h of OFF time per day. Mild infusion site reactions (ISRs) were frequently reported treatment-emergent adverse effects<br><br>Phase 3 trial comparing ND0612 with oral levodopa – ongoing |
| ABBV-951 | Subcutaneous delivery of levodopa/carbidopa phosphate prodrug | Phase 1 study ($n$ = 28) demonstrated steady-state levels and degree of fluctuation similar to LCIG |

# GAIT TREATMENTS

## Transmagnetic Stimulation (TMS) For Freezing of Gait (FOG)

- TMS over supplementary motor cortex confers the beneficial effect by normalizing the abnormal brain functional connectivity pattern

- May serve as an add-on therapy for alleviating FOG in PD patients.

# THE VIBRATING GLOVE

Figure 1

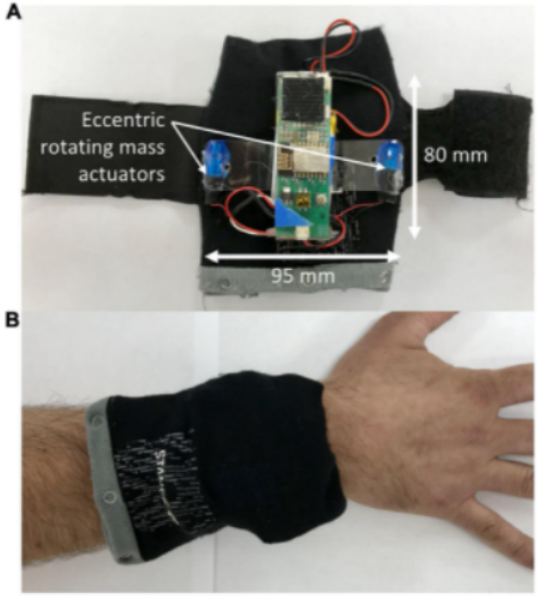



FIGURE 1. The wearable vibrotactile stimulation device. Each vibration unit powered two eccentric rotating mass actuators from which the vibrotactile stimulation was delivered **(A)**. The vibration units were housed in cloth pouches that were attached to the subject's wrists and ankles using a Velcro strap **(B)**.

The device used in the recent Putrino study.

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# Good vibrations

## Can Parkinson's symptoms be stopped?

By Holly Alyssa MacCormick
**Illustration by** Harry Campbell

Artist's conception of a vibrating glove used to help relieve symptoms of Parkinson's.

October 14, 2021

- **Very little data made public, as far as we know no longer placebo control studies have been done**
- **We need more information**

# EXERCISE

- Release of neurotrophic factors and greater cerebral oxygenation
- Stimulates dopamine synthesis for symptom improvement
- Evidence that it improves physical functioning, health-related quality of life, strength, balance and gait speed for people with PD

- Rock Steady Boxing
- Qi Gong
- Feldenkrais
- Cycling
- Dance
- Yoga
- Mindfulness
- Tai Chi
- Stand up paddle boarding

# KAISER PERMANENTE MISSION

- https://parkinsonscare.kaiserpermanente.org/
- Multidisciplinary approach
- A judicious drug formulary
- High standards of care
- A Growing Interest in Integrative Medicine

# CITATIONS


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# THANK YOU