An overview of clinical trials for Parkinson's: Ongoing and the future

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http://www.pdtrialtracker.info

Maintained by Gary Rafaloff & Sue Buff
687 ongoing clinical trials for Parkinson’s
An overview of clinical trials for Parkinson's: Ongoing and the future

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An overview of clinical trials for disease modification in Parkinson's

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What do we mean by “disease modification”? 
Symptomatic
Symptomatic:
“Any medical treatment of a disease that only affects its symptoms, not its cause”
Parkinson's medications:
Dopamine agonists, MAO-B inhibitors, and Levodopa
The normal trajectory of Parkinson’s

First indication something is wrong

Diagnosis

Initiation of symptomatic treatment
Disease modification:
“Any medical treatment of a disease that changes the trajectory of the condition”

A therapy that slows, stops or reverses the disease.
An altered trajectory for Parkinson’s

Initiation of disease modifying treatment

First indication something is wrong

Diagnosis
The Hope list
bit.ly/ParkinsonsHopeList

Dr Kevin McFarthing

<table>
<thead>
<tr>
<th>CLINICAL</th>
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<td>Phase 1</td>
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<td>Phase 2</td>
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<td>Phase 3</td>
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<td>Proof of concept</td>
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<td>Submitted or pre-submission</td>
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<td><strong>TOTAL</strong></td>
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<td>Symptom relief</td>
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<td>Disease modifying</td>
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<td>NCE</td>
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<td>Reformulation</td>
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<td>Repurpose</td>
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<td>Cells</td>
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<td>Gene therapy</td>
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<td><strong>TOTAL</strong></td>
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**PHASES of a CLINICAL TRIAL**

**Preclinical LABORATORY STUDIES**
Duration: Several years
✓ Provide information on dosing and toxicity levels

**Phase 1 SAFETY**
Duration: Several months
✓ Evaluate safety
✓ Gather information about how a drug interacts with the human body

**Phase 2 SAFETY AND DOSING**
Duration: Several months
✓ Further evaluate safety
✓ Monitor side effects
✓ Check which dose works best
✓ Check effectiveness

**Phase 3 SAFETY AND EFFICACY**
Duration: Several years
✓ Confirm effectiveness
✓ Monitor safety

**Phase 4 POST MARKETING SAFETY AND EFFICACY**
✓ Gather information on the drug’s effect in various populations and any side effects associated with long-term use
Disease modifying therapies for Parkinson’s will require one of **three** key components:

1. A disease halting mechanism
2. A neuroprotective agent
3. A cell replacement therapy
Component #1.

A disease halting mechanism
How do we slow/stop this spreading of the condition?
1. Immunotherapy

Harnessing the immune system to target toxic proteins
1. Immunotherapy

PRX002 - Engineered antibodies to target the toxic form of alpha synuclein.

1x phase II trial (300 people; 52 weeks – results due 2020)
1. Immunotherapy

BIIB054 - Phase II study (300+ people; ends in 2022)
1. Immunotherapy

- MEDI1341
- ACI-870
- Lu AF82422
- BAN0805
- PD1601
- PD1602
- UB-31
1. Immunotherapy

**PD01A** - a vaccine to target the toxic form of alpha synuclein. Phase I results suggest it is safe
2. Immunomodulation

Dampening down the immune response
2. Immunomodulation

Sargramostim - bone marrow transplantation treatment

Phase I trial gave interesting results 2017
3. Boosting cellular waste disposal

Increasing the ability of cells to clear toxic rubbish
3. Boosting cellular waste disposal

Ambroxol – a respiratory treatment

Phase II results to be published; Phase III begins 2019
3. Boosting cellular waste disposal

**Venglustat** – a phase II clinical trial (MOVE-PD)

**LTI-291** – being developed by Lysosomal Therapeutics

**RTB101** – Phase I testing ongoing in New Zealand
3. Boosting cellular waste disposal

Nilotinib – a leukemia treatment

Two ongoing phase II trials - results due 2019/20
3. Boosting cellular waste disposal

- IkT-148009
- Radotinib
- K0706
- 1ST-102
4. LRRK2 inhibition

A hyperactive protein associated with Parkinson’s
4. LRRK2 inhibition

Blocking the hyperactive protein

Denali Therapeutics currently conducting a Phase I trial of their LRRK2 inhibitor, DNL-201.
4. **LRRK2 inhibition**

Other companies are also developing LRRK2 inhibitors for Parkinson’s.

[Logos of GSK, Cerevel, SIRION BIOTECH]
Component #1
A disease halting mechanism

- Immunotherapy
- Immunomodulation
- Boost waste disposal
- LRRK2 inhibition
Component #2.

Neuroprotection: A Possible Future Treatment

A neuroprotective agent
GLP1 agonists

Diabetes drugs being repurposed for Parkinson’s
GLP1 agonists - Bydureon/Exenatide

Phase III trial starting in 2019 (reporting in 2023/24)

Athauda et al 2017
GLP1 agonists

3x Phase II trials in France & US (Lixisenatide and Liraglutide)

Semaglutide - Phase II trial in Norway

NLY01 - Setting up for Phase I trial
Other repurposed drugs

**Ursodiol/UDCA**
Gallstones treatment
Phase I safety trial - results due 2019

Phase II trial started in UK

**Simvastatin**
Cholesterol drug

**STAT-PD Phase II trial**
- results due in 2020/21
Neurotrophic factors

Naturally produced protective proteins

Glial cell-derived neurotrophic factor (or GDNF)
Neurotrophic factors

Glial cell-derived neurotrophic factor (or GDNF)

Whone et al (2019)
Neurotrophic factors

Herantis Pharma are currently testing CDNF (Cerebral Dopamine Neurotrophic Factor) in a clinical trial.

18 participants.

Results in mid 2020.
Component #2
Neuroprotective treatment
- GLP1 agonists
- Repurposed drugs
- Neurotrophic factors
Component #3.

A cell replacement approach
Cell transplantation therapy

Parkinson’s is associated with the progressive loss of dopamine neurons in the midbrain…
Cell transplantation therapy

...which results in the loss of dopamine fibres in the putamen
Cell transplantation therapy

Previous clinical studies indicate that we can replace dopamine fibres in the putamen.
There are currently 5 clinical trial programs for cell transplantation ongoing or starting this year.

And more research groups are seeking to start.
Future directions – gene therapy

Treating people with DNA rather than drugs
Future directions – gene therapy

Gene therapy clinical trials for Parkinson’s are ongoing.
Future directions – gene therapy

Gene therapy approaches for disease modification in Parkinson’s are also being developed.

A gene therapy trial for GDNF is also ongoing.
Future directions – gene therapy

The 21st century gold rush – non-invasive gene therapy.
Future directions – sub-types
Future directions – Prodromal

Treating people before they get Parkinson’s.

- Time (years)
  - -20
  - -10
  - 0
  - 10
  - 20

- Degree of disability
- Pre-motor/prodromal period
- Parkinson’s disease diagnosis
  - Early
  - Advanced/late
- Complications
  - Dysphagia
  - Postural instability
  - Freezing of gait
  - Falls
- Motor
  - Bradykinesia
  - Rigidity
  - Tremor
- Non-motor
  - Constipation
  - RBD
  - EDS
  - Hyposmia
  - Depression
  - Pain
  - Fatigue
  - MCI
  - Urinary symptoms
    - Orthostatic hypotension
    - Dementia
What is going to work?
1. It depends on the type of Parkinson’s each individual has.
1. It depends on the type of Parkinson’s each individual has.

2. I do not expect any of these treatments to work.
Expectations

Reality
KEEP CALM AND LOWER YOUR EXPECTATIONS
‘Positive realism’
Reasons for optimism?
107,000 “Parkinson’s”-related research reports

83,000 of them have been published in the last 20 years.
Summary:
There are multiple approaches being applied to the core components for disease modifying therapies for Parkinson’s:

1. A disease halting mechanism

2. A neuroprotective agent

3. A cell replacement therapy
Thank you very much

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