A Bird Cannot Fly With One Wing

Clinical Trials in Parkinson’s Disease
Moving Forward February 12, 2018
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Detling Professor and Chair
Animal Research Saves Lives
Learning objectives

• Parkinson’s basics
• Treatment basics
• Preclinical research—identifying targets
• Clinical research
Parkinson’s basics
Parkinson’s disease: a complex disease

http://pn.bmj.com/content/14/5/310
From protein to disease

Alpha-synuclein protein aggregation

Oxidative stress
Energy failure
Excitotoxicity
Transport failure
Interference with other genes
Interference with proteins

Death of dopamine neurons
Death of other neurons
Dopamine ↓

Other neurochemical ↓
“nonmotor PD”
The progression of Parkinson’s disease

Over time, new brain areas & chemicals become affected by the degenerative process

Braak et al.
So many neurochemicals

<table>
<thead>
<tr>
<th>Neurochemical</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine</strong></td>
<td>Tremor, rigidity, slowness; color vision; visual contrast; ↓ standing BP</td>
</tr>
<tr>
<td><strong>Norepinephrine</strong></td>
<td>Depression; REM behavior disorder; ↓ standing BP</td>
</tr>
<tr>
<td><strong>Acetyl choline</strong></td>
<td>REM behavior disorder; cognitive impairment; ↓ smell; ↓ standing BP; ↓ swallow; bloating; gas; constipation</td>
</tr>
<tr>
<td><strong>Serotonin</strong></td>
<td>Depression; REM behavior disorder</td>
</tr>
<tr>
<td><strong>Glutamate</strong></td>
<td>Cognitive impairment; ↓ balance; slowness</td>
</tr>
</tbody>
</table>
Treatment basics
Symptomatic treatments of PD

Dopamine-responsive symptoms

Stimulate dopamine-sensitive structures = “receptors”

Deep Brain Stimulation

Increase brain dopamine
Carbidopa/levodopa

Diagram showing the metabolism of L-DOPA: L-DOPA is converted to dopamine in the brain, with 10% of L-DOPA entering the bloodstream. Carbidopa is shown to inhibit the decarboxylase enzyme, preventing the conversion of L-DOPA to dopamine in the blood and intestines.
Identifying better **symptomatic** therapies

Rotigotine
Pramipexole
Ropinirole

3-MT
COMT
DOPA
L-DOPA
Dopamine
DOPAC
MAO-B
Selegiline
Rasagiline

Blood-
Brain
Barrier

L-amino acid transporter

Brain

Blood

Side effects:
- nausea/vomiting (CTZ)
- arrhythmias
- postural hypotension

Tolcapone
Entacapone
Carbidopa
Biology of disease...target identification
preclinical research
Clinical Research

What is a clinical trial?

- Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

World Health Organization

- Drugs
- Cells, biological products
- Surgical procedures
- Devices
- Behavioral treatments
- Process-of-care changes
- Preventive care
- Etc.
Alpha-synuclein protein aggregation
Death of dopamine neurons
Dopamine ↓
- Tremor
- Rigidity
- Bradykinesia
- Postural instability

Oxidative stress
Energy failure
Excitotoxicity
Transport failure
Interference with other genes
Interference with proteins

Other neurochemical ↓
“nonmotor PD”

Neuroprotection/disease modification
Symptomatic
Clinical research studies, especially clinical trials, are how *new knowledge* is generated, and they help to find *new treatments*. Being a research participant is not for everyone, but **without participants there cannot be new treatments in the future.** [http://www.huntington-study-group.org](http://www.huntington-study-group.org)
How many years to a cure?

Drug development

Years

0
Discovery (2–10 Years)

2
Preclinical Testing
Laboratory and Animal Testing

4
Phase I
20–80 Healthy Volunteers Used to Determine Safety and Dosage

6
Phase II
100–300 Patient Volunteers Used to Look for Efficacy and Side Effects

8
Phase III
1,000–5,000 Patient Volunteers Used to Monitor Adverse Reactions to Long-Term Use

10
Additional Post-Marketing Testing

12
FDA Review Approval

14

16

Compound Success Rates by Stage

5,000–10,000 Screened

250 Enter Preclinical Testing

5 Enter Clinical Testing

1 Approved by the FDA
Oversight of Clinical Research in US
Phase 1
• A Phase 1 trial usually is a small group of participants that are testing the safety of the supplement, drug or treatment.

Phase 2
• A Phase 2 trial tests the supplement, drug or treatment for safety and best dosage in a small group of participants who have the specific disease.

Phase 3
• Tests for effectiveness of the supplement, drug, or treatment in a larger group with the specific disease. Usually at least two Phase 3 trials need to be completed to convince the FDA that the drug is safe and effective.

Phase 4
• A Phase 4 trial is also called an “after market” study which means that companies collect data on safety and effectiveness after the drug has been approved by the FDA and is available to many more patients.
Food & Drug Administration New Drug Approval

• Is the drug safe and effective?
  • Requires substantial evidence of effectiveness demonstrated through controlled clinical trials.
    • Randomized, double-blind, placebo-controlled studies are typically required

• Do the benefits outweigh the risks?

• Is the package insert appropriate and complete?

• Are the methods used in manufacturing and controls to maintain quality adequate
Clinical Trial Protocol

• Purpose of the study
• Background and rationale

• Research Methods
  • Study design (e.g. “randomized, placebo-controlled...”)
  • Study population
    • Inclusion criteria (e.g. diagnosis, duration, severity, age...)
    • Exclusion criteria (e.g. medications, other illnesses...)
  • Study intervention (e.g. dose, dose interval...)
  • Study assessments (e.g. rating scales, cognitive tests, imaging studies, blood work)

• Method of analysis
Institutional Review Board

- Group formally designated to review and monitor biomedical research involving human subjects at an institution
- Written “assurance” that the institution will comply with HHS protection of human subjects
- Initial approval, approval of any subsequent changes (amendment), annual approval
## Clinical Trial Protocol

### Schedule of activities

<table>
<thead>
<tr>
<th>Survey item</th>
<th>Observation Periods (At least 2 weeks)</th>
<th>The periods of the increase in dose and of concomitant use</th>
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</thead>
<tbody>
<tr>
<td>Evaluation of the eligibility of the subjects</td>
<td></td>
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<tr>
<td>Enrollment of informed consent</td>
<td></td>
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<tr>
<td>Enrolment of the subjects</td>
<td></td>
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<tr>
<td>The dose of the study drug is increased or antihypertensive drug is additionally used with the study drug</td>
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<tr>
<td>Survey of patient background</td>
<td></td>
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<tr>
<td>Confirmation of other concomitant drug and combined therapy</td>
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<td></td>
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<tr>
<td>Height</td>
<td></td>
<td></td>
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<tr>
<td>Body weight</td>
<td></td>
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<tr>
<td>Blood pressure levels measured (in a sitting position) on an outpatient basis: Heart rate</td>
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<tr>
<td>Echocardiography</td>
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<tr>
<td>Echography of the cervical artery</td>
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<td>Pulse wave velocity (PWV)</td>
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<td>Fundoscopy</td>
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<td>Electrocardiography (ECG)</td>
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<tr>
<td>Chest X-ray radiography</td>
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<tr>
<td>Hematology Tests</td>
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<tr>
<td>Hemoglobin</td>
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<tr>
<td>Blood pressure levels measured (in a sitting position)</td>
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<tr>
<td>Urea nitrogen</td>
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<tr>
<td>Creatinine</td>
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<tr>
<td>Liver function test</td>
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<tr>
<td>Urinary albumin level (calculated in creatinine equivalent)</td>
<td></td>
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<tr>
<td>Other items</td>
<td></td>
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<tr>
<td>Confirmation of events and adverse events</td>
<td></td>
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<tr>
<td>Survey of the evaluation of medical cost-effectiveness</td>
<td></td>
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<tr>
<td>Blood pressure levels measured at home (in a sitting position after getting up and before going to bed)</td>
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</tbody>
</table>
Elements of informed consent

1. Study involves research
2. Purpose of research
3. Expected time to participate
4. Description of all procedures
5. Information on experimental procedures
6. Any predictable risks
7. Any possible discomforts
8. Any potential benefits
9. Any alternatives to participating
10. Description of confidentiality
    • Confidentiality of collected data
    • How records will be kept
    • FDA may inspect records
11. Whether compensation or treatment are available for injury
12. How to get answers to questions about research
13. Research subject’s rights
14. Injury related to trial
15. Research is voluntary
Elements of informed consent

16. Subjects have the right to refuse participation without losing any benefits

17. Subjects may stop participation without losing any benefits

18. Contact information for study

19. Anticipated risks to unborn fetus

20. Reasons participation may be stopped by investigator

21. Added costs resulting from trial participation

22. Consequences that may result from stopping study participation

23. Statement that subject will be informed of new information that may affect willingness to continue.

24. Approximate number of subjects who will participate in the study.
Clinical trials

Keeping informed about clinical trials
Current PD trials in US
Phase II and Phase III

Clinicaltrials.gov
12/27/2017
Clinicaltrials.gov
Symptomatic treatments (examples)

- RDBPC study of *liguratide* (injection) (Cedars Sinai, Los Angeles); Θ2
  - 57 PD subjects
- RDBPC study of *varenicline* for gait and balance (Rush, Chicago); Θ2/3
  - 40 PD subjects
- RDBPC crossover study of *L-dihydroxyphenylserine* for gait/balance/falls (Barrow, Phoenix); Θ2/3
  - 20 PD subjects
- RDBPC study of *cannabidiol* for tremor (U Colorado, Denver); Θ2
  - 60 PD subjects (10 safety/dose; 50 efficacy)
- OL study of *ropinirole implant* (U Rochester, Rochester NY); Θ1/2
  - 20 PD subjects

Clinicaltrials.gov
12/27/2017
Disease-modifying treatments (examples)

- **RDBPC BIIB054 intravenous** (Orlando, Tampa FL; Farmington Hills MI; Spokane WA); Θ2
  - 311 PD subjects

- **OL EPI-589** (Los Angeles, San Francisco CA; Boston MA; Tuebingen Germany; London UK); Θ2
  - 40 PD subjects

- **DBPC nilotinib** (Phoenix AZ; Denver CO; Gainesville FL; Tampa FL; Lexington KY; Baltimore MD; Ann Arbor MI; Las Vegas NV; Albany NY; NY NY; Durham NC; Cleveland OH; Philadelphia PA; Houston TX; Milwaukee WI); Θ2
  - 135 PD subjects
Critical evaluation of media reports on PD research
Exenatide

- 62 moderate PD subjects
- RDBPC study
  - Exenatide 2mg vs placebo injection (SQ)
  - 48 weeks, 12 week washout
- 1 point better
- 2 points worse

“The trial on 62 patients, published in the Lancet, hints the medicine halted the progression of the disease”
How the data are presented...

Extend scale to 0...

Include full range of scale...

Statistical significance may not translate to clinical significance...
Significance...

Statistical significance...
• A number that expresses the probability that the result of a given experiment could have occurred purely by chance.
• P value 0.05 means that there is a 5% chance the differences between the groups could have occurred simply on the basis of chance.

Clinical significance...
• The practical importance of a treatment effect—whether it has a real, noticeable effect on daily life.
• The minimal clinically important difference on motor MDS-UPDRS
  • Improvement: 3.25 points
  • Decline: 4.63 points
“...compared with placebo, exenatide treatment is associated with positive and persistent effects on off-medication motor scores as measured by MDS-UPDS part 3. Whether this drug acts as a novel symptomatic agent, influences compensatory responses or behaviors, or has neuroprotective effects on underlying pathology is unclear...”
Study design

Sample size in each group (assumes equal sized groups)

\[ n = 2 \times \frac{\sigma^2 (Z_{\beta} + Z_{\alpha/2})^2}{\text{difference}^2} \]

Represents the desired power (typically .84 for 80% power).

Standard deviation of the outcome variable

Effect Size (the difference in means)

Represents the desired level of statistical significance (typically 1.96).
RESEARCHERS REPORT FIRST THERAPY APPEARING TO REVERSE DECLINE IN PARKINSON’S

- 12 PDD/DLB patients
- Open label trial
  - 150 or 300 mg
  - 24 weeks
- Results
  - Possible beneficial effects
    - Reversed when drug stopped
  - Motor & cognitive measures
  - Interpret with caution
  - Further testing needed

From clinicaltrials.gov
- MJFF study
- 135 subjects
  - 150 mg, 300 mg, placebo

Journal of Parkinson Disease 2016;6:503
The actual data...convinced?
How to recognize research “scams”

**Baloney detection**
- Cure all
- Personal testimonials
- Quick fixes
- All natural
- Miracle cure
- Conspiracy theories
- Cost
Clinical trials are starting at UW!!

- A trial of subcutaneous levodopa pump for PD subjects with motor fluctuations.....
- A trial of an investigational agent for cognitive impairment in PD......
Questions?