Parkinson’s disease: Research Advances & Updates

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October 1, 2016
Parkinson’s disease – 2016

- Genetics
- Pathophysiology
- Biomarkers
- Diagnosis
- Treatment
Genetics

• About 15% of PD is thought to be caused by genetics—primarily SNCA and LRRK2 mutations.

• Mutations in the TMEM230 gene were pathologically and clinically proven to cause PD.

• Gene encodes a protein that extends across the membrane of synaptic vesicles.
Gene>
cs

• PD patients with and without LRRK2 showed Miro protein dysfunction.

• Miro is removed when mitochondria aren’t working well and need to be recycled.

• LRRK2 dysfunction prevents Miro removal, which slows the recycling process and may harm the cell.
Pathophysiology

- L-DOPA in LID animal model increased expression of two DNA demethylases, especially in dorsal striatum cells.

- Changes in DNA methylation were near many genes thought to have functional importance in LID.

- Applying medications that increased DNA methylation improved LID.
Pathophysiology

- Using fMRI, PD shown to have reorganization of their functional brain networks and L-DOPA tends to normalize these networks.
Biomarkers

- A biomarker is something that helps physicians predict, diagnose or monitor a disease.
- Sensitive technology that measures the stickiness of proteins called “real-time quaking induced conversion” in early tests was able to correctly identify PD in 19 of 20 patients.
Biomarkers

• Elevated phosphorylated LRRK2 in urine predicted the risk for onset of PD for people carrying a LRRK2 mutation
Diagnosis

• In a rat PD model, changes in the eye were detected before motor symptoms appeared using a new technique of shining light on the back of the eye.

• Eye changes include number of retina (retinal ganglion cells), are going through cell death, as well as signs of swelling in the region.

Fig. 1.1. A drawing of a section through the human eye with a schematic enlargement of the retina.
Treatment: Motor

• Positive results from Phase II trial under-the-tongue strip, apomorphine reformulation, for OFF rescue therapy (APL-130277).

• Positive results from Phase IIb trial of self-administered, inhaled L-DOPA) therapy for the episodic treatment of OFF periods (CVT-301).
Treatment: Motor

- Long-acting amantadine formulation led to a significant reduction in LID at 12 weeks and about to be submitted for FDA approval (ADS-5102).

Treatment: Motor

• Open label study of Intec Accordion CL formulation gastroretentive platform (enrolling soon).

• Effect of medical marijuana (cannabidiol) on tremor in PD (enrolling soon).
Treatment: Motor

- Botulinum toxin B injections for bothersome drooling (enrolling).
- Collagen injections in vocal folds for voice and speech impairment in PD (enrolling).
Treatment: Non-motor

- Study of droxidopa for orthostatic hypotension (enrolling).
- Music Therapy for Dementia (enrolling).
- Research study of thinking, memory, and everyday functioning in PD and PD dementia (enrolling).
- Research study of outpatient palliative care in PD (enrolling).
Treatment: Neuroprotective

• The Safety of Urate Elevation in Parkinson's Disease Phase III study (SURE-PD3), which is testing whether inosine elevates urate in PD and slows progression (enrolling).

• Study of phenylbutyrate to clear alpha-synuclein from the brain and slow PD (enrolling soon).
Treatment: Neuroprotective

- Early clinical trial of vaccine for PD (PD01A) in 24 early-stage PD patients showed vaccine safe and half of patients created antibodies to alpha-synuclein.
- Results from vaccine “boost” study supported its continued development in PD.
Treatment: Neuroprotective

- Multicenter study of PARkinson’s disease and eXercise (SPARX) just completed.
- Results out soon on effect of endurance training in early, untreated PD.
From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of $2.6 billion.* Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.

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* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

## Parkinson’s Disease

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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Drug/Intervention</th>
<th>PI/Coordinator</th>
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<tr>
<td><strong>Palliative Care</strong></td>
<td>PD with palliative care needs (e.g. nonmotor symptoms, caregiver distress, psychosocial issues)</td>
<td>Usual care vs outpatient palliative care clinic for 12 months</td>
<td>Kluger/Etta Abaca <a href="mailto:Etta.abaca@ucdenver.edu">Etta.abaca@ucdenver.edu</a> 303-724-4718</td>
</tr>
<tr>
<td><strong>Myobloc Injections for Treatment of Sialorrhea</strong></td>
<td>PD/non-PD subjects with excessive drooling &gt;3 months</td>
<td>Salivary gland injections every 13 weeks for a total of 5 treatments</td>
<td>Klepitskaya/Lindsay Hosford <a href="mailto:Lindsay.hosford@ucdenver.edu">Lindsay.hosford@ucdenver.edu</a> 303-724-6247</td>
</tr>
<tr>
<td><strong>Apomorphine Infusion</strong></td>
<td>PD with &gt;2 hours off time on levodopa</td>
<td>Apomorphine infusion 15 visits over 1 year + indefinite extension</td>
<td>Klepitskaya/Lindsay Hosford <a href="mailto:Lindsay.hosford@ucdenver.edu">Lindsay.hosford@ucdenver.edu</a> 303-724-6247</td>
</tr>
<tr>
<td><strong>Brain changes underlying PD</strong></td>
<td>PD – cognitively intact, on dopaminergic med</td>
<td>Exam and MRI scans before and after L-Dopa 2 visits (1.5 hr and 3 hr)</td>
<td>Berman/Erika Shelton <a href="mailto:Erika.shelton@ucdenver.edu">Erika.shelton@ucdenver.edu</a> 303-724-5865</td>
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<td><strong>Ongoing enrollment</strong></td>
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<td><strong>Cognitive Functional Ability in PD</strong></td>
<td>PD – normal cognition, PD-MCI and PDD Any meds, DBS okay</td>
<td>One 3-4 hour visit for neuropsych testing and a performance-based ADL assessment</td>
<td>Holden/Luis Medina <a href="mailto:Luis.medina@ucdenver.edu">Luis.medina@ucdenver.edu</a> 303-724-9605</td>
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<tr>
<td><strong>Rhythm and Motor Processing</strong></td>
<td>PD – No DBS (PD patients no longer needed, looking for male controls between 70-85 years old)</td>
<td>2 hours fMRI one visit in Boulder</td>
<td>Kluger/Kurt Braunlich <a href="mailto:kbraunlich@gmail.com">kbraunlich@gmail.com</a> 360-535-3495</td>
</tr>
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<td><strong>Visual, Vestibular, Oculomotor Deficits &amp; Fatigue and Balance in PD</strong></td>
<td>PD</td>
<td>2 visits (in a 2 week period) assess eye movements, balance &amp; fatigue 1st visit: 3 hours 2nd visit: 1.5 hours</td>
<td>Schenkmann/Jan Berlinger <a href="mailto:Jean.berliner@ucdenver.edu">Jean.berliner@ucdenver.edu</a> 303-724-7888</td>
</tr>
<tr>
<td><strong>Orthostatic Hypotension - Droxidopa</strong></td>
<td>Symptomatic NOH due to PD, MSA, PAF, NDAN or DBH deficiency; BP drop of &lt;20mmHg after standing 3 min</td>
<td>4 weeks of up to 5 titration visits, then 3 months of open-label (3 visits) followed by 3 months of double blind placebo controlled (6 visits)</td>
<td>Klepitskaya/Lindsay Hosford <a href="mailto:Lindsay.hosford@ucdenver.edu">Lindsay.hosford@ucdenver.edu</a> 303-724-6247</td>
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<td>Rhythm and Motor Processing</td>
<td>PD – No DBS</td>
<td>1 hour MRI, 2 hour MEG</td>
<td>Kluger/Isabelle Buard</td>
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<td>TMS for PD Cognitive Impairment</td>
<td>PD with MCI- No DBS</td>
<td>MRI, MEG, 2 weeks of daily TMS treatments, Neuropsych testing</td>
<td>Kluger/Isabelle Buard</td>
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<tr>
<td>Phenylbutyrate</td>
<td>PD – not on meds</td>
<td>Phenylbutyrate (liquid)</td>
<td>Freed/Gabrielle Lehmicke</td>
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<tr>
<td>Will start recruiting in late 2016, coordinator will call with information</td>
<td>PD not on meds or only on MAOB-I</td>
<td>Visits over 1 year</td>
<td><a href="mailto:Gabrielle.Lehmicke@ucdenver.edu">Gabrielle.Lehmicke@ucdenver.edu</a></td>
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<tr>
<td>Inosine</td>
<td></td>
<td>Inosine, 1 year</td>
<td>Klepitskaya, Leehey/Lindsay Hosford</td>
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<tr>
<td>Enrolling in Summer 2016</td>
<td>PD with tremor</td>
<td>4 visits over 10 weeks</td>
<td>Leehey/Lingy Liu</td>
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<td>Marijuana in PD – Stage 1</td>
<td>PD with tremor</td>
<td>8 visits over 22 weeks</td>
<td>Leehey/Lingy Liu</td>
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<td>Enrolling in July 2016</td>
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<tr>
<td>Marijuana in PD – Stage 2</td>
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<td>Enrolling in July 2016</td>
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Thank you