Overcoming Parkinson Disease

Emerging Therapies

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Symptomatic therapies

Hara et al., Br J Pharmacol. 2018
Disease Modifying

- Disease-modifying therapies refer to strategies intended to:
  - Prevent
  - Slow
  - Halt progression

- Strategies include:
  - Reducing oxidative damage or inflammation
  - Promoting neuronal support
  - Targeting abnormal proteins
  - Avoiding spread of disease

### Antioxidant
Too much oxidation may lead to neuronal death in PD.

- Glutathione
- Inosine

### Neurotrophic Factors
Trophic factors are like the brain’s natural fertilizer; they help restore and protect neurons.

- GDNF
- CERE-120

### Alpha-synuclein
This toxic protein clumps in the brains of PD patients.

- Affitope
- NPT088
- NPT200-11

### Repurposed Compounds
Some natural elements or drugs approved for other conditions could be beneficial for PD patients.

- Exenatide (Byetta)
- Isradipine
- Nicotine Patch
- Nilotinib

From MJFF
Antisense oligonucleotides

β2-adrenoceptor stimulation

Targeting α-synuclein aggregation

Increase GCase activity

Immunotherapy to target α-synuclein

Intrabody targeting of α-synuclein

Modified from Hara et al., Br J Pharmacol. 2018
How does PD spreads?

Information is transmitted as a template that changes the configuration of normal proteins in preserved cells.

From Marc Diamond
How PD spreads?

Propagation of Abnormal Configuration

From Marc Diamond
- 50% neuron loss in the substantia nigra (SN) at dx
- 80% striatal dopamine is lost by dx
Subpart E

- CFR (Code of Federal Regulations) establishes procedure to expedite the development, evaluation and marketing of new therapies intended to treat people with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternatives exist.
Drug development

- Cost of bringing a new molecule to market is ≅ $2.6 billion
- Takes ≅ 13–15 years
- Only 11.3% of drugs entering clinical testing make it to the market
- New drugs approved by the FDA per billion USD spent on R&D has been reduced to one-half every 9 years since 1950
- Repurpusing is using old drugs for new applications
- Cost ≅ 300 million USD and takes ≅ 6.5 years

Repurposing drugs: "Old wine in New bottles"

Kakkar et al, 2018
<table>
<thead>
<tr>
<th>Drug name or class</th>
<th>Approved therapeutic use/physiological role</th>
<th>Proposed mode of action in PD</th>
<th>Preclinical studies</th>
<th>Clinical studies/trials</th>
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<tbody>
<tr>
<td>Glucagon-like peptide-1 (GLP-1) receptor agonists &amp; Dipeptidyl peptidase-4 (DPP-4) inhibitors</td>
<td>Type 2 Diabetes Mellitus</td>
<td>Target neuroinflammation, mitochondrial dysfunction, oxidative stress, protein aggregation and neurogenesis.</td>
<td>Harkavy et al., 2008 Bertilsson et al., 2008 Kim et al., 2009 Li et al., 2009 Ventorp et al., 2017 Liu et al., 2015 Hansen et al., 2016 Badawi et al., 2017 Nassar et al., 2015 Ribeiro et al., 2012 Abdelsalam and Safar, 2015</td>
<td>Aviles-Olmos et al., 2013 Aviles-Olmos et al., 2014 Athauda et al., 2017a Svenningsson et al., 2016 NCT03456687, NCT02953665, NCT03439943</td>
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<td>Beta-2 adrenergic receptor agonists</td>
<td>Treatment or prevention of bronchospasm</td>
<td>Reduced SNCA gene expression and mitochondrial free radicals; inhibition of microglial activation</td>
<td>Mittal et al., 2017 Qian et al., 2011</td>
<td>Mittal et al., 2017 Uc et al., 2003 Alexander et al., 1994b Pagan et al., 2016, NCT02954978, NCT03205488</td>
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<td>Nilotinib</td>
<td>Philadelphia chromosome positive chronic myelogenous leukemia</td>
<td>Degradation of misfolded α-synuclein via autophagy; increased Parkin activity</td>
<td>Tanabe et al., 2014 Hebron et al., 2013 Karuppagounder et al., 2014</td>
<td>Carroll and Wyse, 2017 a, NCT02787590</td>
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<tr>
<td>Simvastatin</td>
<td>Hypercholesterolemia</td>
<td>Inhibition of proinflammatory molecules, microglial activation, α-synuclein aggregation, oxidative stress; upregulation of endothelial NOS, neurotrophic factors</td>
<td>Ghosh et al., 2009 Selley, 2005 Yan et al., 2011</td>
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<td>Ambroxol</td>
<td>Mucolytic therapy in productive cough in acute/ chronic bronchopulmonary conditions associated with abnormal mucus production and diminished mucus transport. Not approved for use in US/ UK</td>
<td>Increased glucocerebrosidase enzyme activity</td>
<td>Migdalska-Richards et al., 2016 Migdalska-Richards et al., 2017 Whitworth et al., 2016</td>
<td>NCT02914366, NCT02941822</td>
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<td>Deferiprone</td>
<td>Transfusional iron overload</td>
<td>Removal of excess iron from substantia nigra pars compacta leading to attenuation of reactive oxygen species generation and α-synuclein aggregation</td>
<td>Dexter et al., 2011 Zhu et al., 2017 Devos et al., 2014</td>
<td>Devos et al., 2014 Grolez et al., 2015 Dexter et al., 2013 Martin-Bastida et al., 2017 NCT02728843, NCT02655315, NCT02880033 de Lau et al., 2005 Weisskopf et al., 2007 Gao et al., 2016 Wen et al., 2017 Ascherio et al., 2009 Parkinson Study Group SURE-PD Investigators et al., 2014 NCT02642393 Simuni et al., 2010 Parkinson Study Group, 2013 Biglan et al., 2017 NCT02168842</td>
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<tr>
<td>Inosine</td>
<td>Breakdown product of adenosine with proposed neuroprotective, cardioprotective and immunomodulatory effects.</td>
<td>Elevation of serum and cerebrospinal fluid urate levels that confer neuroprotection through antioxidant and metal chelation properties</td>
<td>Gong et al., 2012 Zhang et al., 2014</td>
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<tr>
<td>Isradipine</td>
<td>Hypertension</td>
<td>Inhibition of L-type voltage gated calcium channels responsible for selective vulnerability of dopaminergic neurons in substantia nigra pars compacta</td>
<td>Chan et al., 2007 Ilijic et al., 2011</td>
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<td>Kakkar et al, 2018</td>
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Exenatide once weekly versus placebo in Parkinson’s disease: a randomised, double-blind, placebo-controlled trial

Dilan Athauda, Kate Maclagan, Simon S Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Luca Zampedri, John Dickson, Yazhou Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H Greig, Susan Tebbs, Thomas Foltynie

Summary

Background Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has neuroprotective effects in preclinical models of Parkinson’s disease. We investigated whether these effects would be apparent in a clinical trial.

Methods In this single-centre, randomised, double-blind, placebo-controlled trial, patients with moderate Parkinson’s disease were randomly assigned (1:1) to receive subcutaneous injections of exenatide 2 mg or placebo once weekly for 48 weeks in addition to their regular medication, followed by a 12-week washout period. Eligible patients were aged 25–75 years, had idiopathic Parkinson’s disease as measured by Queen Square Brain Bank criteria, were on dopaminergic treatment with wearing-off effects, and were at Hoehn and Yahr stage 2.5 or less when on treatment. Randomisation was by web-based randomisation with a two strata block design according to disease severity. Patients and investigators were masked to treatment allocation. The primary outcome was the adjusted difference in the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) motor subscale (part 3) in the practically defined off-medication state at 60 weeks. All efficacy analyses were based on a modified intention-to-treat principle, which included all patients who completed any post-randomisation follow-up assessments. The study is registered at ClinicalTrials.gov (NCT01971242) and is completed.

Findings Between June 18, 2014, and March 13, 2015, 62 patients were enrolled and randomly assigned, 32 to exenatide and 30 to placebo. Our primary analysis included 31 patients in the exenatide group and 29 patients in the placebo group. At 60 weeks, off-medication scores on part 3 of the MDS-UPDRS had improved by 1.0 points (95% CI −2.6 to 0.7) in the exenatide group and worsened by 2.1 points (−0.6 to 4.8) in the placebo group, an adjusted mean difference of −3.5 points (−6.7 to −0.3; p=0.0318). Injection site reactions and gastrointestinal symptoms were common adverse events in both groups. Six serious adverse events occurred in the exenatide group and two in the placebo group, although none in either group were judged to be related to the study interventions.

Interpretation Exenatide had positive effects on practically defined off-medication motor scores in Parkinson’s disease, which were sustained beyond the period of exposure. Whether exenatide affects the underlying disease pathophysiology or simply induces long-lasting symptomatic effects is uncertain. Exenatide represents a major new avenue for investigation in Parkinson’s disease, and effects on everyday symptoms should be examined in longer-term trials.
STEADY-PD Isradapine Trial

- Randomized Isradapine placebo-control 2 ½ half year study
- Calcium channel blocker
- Efficacy in slowing PD progression
- 336 early PD patients enrolled
- 50% have completed the study, study will finish by the end of 2018
- Results by mid 2019
SURE-PD Inosine Trial

- Randomized Inosine placebo-control 2 ½ half year study
- Uric acid—antioxidant
- Efficacy of increase in uric acid in slowing PD progression
- Recruited 290 subjects
Nilotinib: inhibiting tyrosine kinase activity

- Nilotinib is an FDA-approved medication for Chronic Leukemia from Novartis, penetrates the brain, protects neurons in animal models

- Inhibits aggregation of synuclein

  - Phase I trial of 12 patients with PD (open label, no placebo) at Georgetown showed positive findings

  - 10 of 12 patients in an Open trial showed is safe and may have clinical improvement (reduced falls, improved cognition, improvement motor function reduced need for dopamine, etc.)

  - Spinal fluid testing showed reductions in toxic proteins found in PD, suggesting that they were being cleared

- Phase II randomized trial ongoing at Georgetown has already recruited \( \approx 80 \) PD subjects mid-stage disease (NCT03205488)
1. NPT200-11
   - Binds to specific $\alpha$-synuclein regions and can prevent its brain toxic effects
   - In PD animal models showed decreased $\alpha$-synuclein accumulation & improvement of motor function (MJFF)-
   - Phase I was being accomplished but no publications and no further info since 2016

2. NPT088
   - Most promising candidate in this class of drugs--binds to several toxic misfolded proteins including $\alpha$-synuclein, tau and $\beta$-amyloid and prevent its brain toxic effects
   - Combines a human immunoglobulin backbone with a General Amyloid Interaction Motif (GAIM)

3. Gene 3 protein (g3p) of filamentous bacteriophage
   - Has shown promise in a mouse PD model where it binds to $\alpha$-synuclein aggregates and prevents brain toxicity
Relevance: Gut Microbiome

Graphical Abstract

Motor dysfunction and pathology
Disease-competent microglia
Short chain fatty acid signaling
Typical Microbiota

Limited pathophysiology
No short chain fatty acid signaling
Germ-free

Enhanced motor dysfunction
Unreactive microglia
PD-derived Microbiota
Therapeutic Clinical Trials
Efficacy, and Safety of glucosylceramide (GL-1) in PD with a GBA Gene Mutation (MOVES-PD)

- Glucosylceramide (GL-1) Genzyme, a Sanofi Company

- Stimulates glucocerebrosidase deficient in PD with GBA mutations

- 168 weeks:
  - 6.5 weeks of screening period
  - 52 weeks of oral treatment period
  - 104 weeks of follow-up period
  - 6 weeks of post-treatment observation period

- Upcoming at UCSD
Immunotherapy

- Antibodies is an exciting development in PD treatment
- Antibodies target the $\alpha$-synuclein deposits that build up in the brain and lead to the symptoms of PD
- Antibodies help the immune system to better recognize these deposits and clear them out
- If/when successful at reducing $\alpha$-synuclein, this has the potential to slow or even stop PD
Passive Immunotherapy

- **Prothena/Roche**
  - Phase Ib trial showed safety & reduced levels (up to 97%) of $\alpha$-synuclein in the blood
  - Phase II randomized placebo-control study is recruiting 300 patients
  - Will start at UCSD at the end of June, 2018

- **Biogen**
  - Phase I showed safety and tolerability
  - Phase II trial will start recruitment in October at UCSD
Active Immunotherapy

AFFiRiS vaccine

- Phase Ib trial showed safety and activation of an immune response in 19 of 22 (86%) of subjects

- Exploratory analyses showed that 8 of the responders did not require increased dopamine for a period of up to 3 yrs
  - Testing a boost in same patients phase I
  - Phase II being planned to be launched in Europe
Personalized Medicine

A

Genetic Risk of PD at age 60 years

SNCA multiplication
PINK1 Q456X
LRRK2 G2019S/R1441C

Susceptibility factors

Percentage of PD patients

0
100

Sporadic

B

PDiPS phenotypes segmentation and clinical symptoms

Genetic group 1
Genetic group 2
Genetic group 3
Genetic group 4

Sporadic PD patient iPS cells

Drug Therapy & Therapeutic Screening
**Stem Cells**

- Provides the potential to provide continuous endogenous dopamine
- Doesn’t treat the non-dopamine symptoms or
- Doesn’t reverse disease progression, exaggerated claims made
- Not new, not regulated, many challenges need to be overcome before translating into humans and many fake salesmen abound
- If interested, participate in a therapeutic trial (for free)
  - Induced pluripotent stem (iPS) cells will start at the end this year in Kyoto University Hospital, Kyoto, Japan
  - Stem cells from fertilized embryos starting in Zhengzhou, China
Before starting a stem-cell PD trial we need to know:

1. What is being transplanted, and what is the proposed mechanism of action?

2. What are the pre-clinical safety and efficacy data supporting the use of the proposed stem cell product?

3. Can arguments concerning ethics, risk mitigation, or trial logistics outweigh concerns regarding the expected efficacy of the cell and constitute a primary justification for choosing one cell type over another in a clinical trial?

4. What is being claimed regarding the potential therapeutic value of the stem cell-based therapy — better control of symptoms or a cure?

5. What is the regulatory oversight of the trial and is it guided by input from experts in the field?

Barker et al., 2016
Altman Clinical & Translational Research Institute (ACTRI)
Conclusions

1. Emerging therapies are directly or indirectly targeting α-synuclein to slow disease progression

2. Therapies are attempting to avoid α-synuclein:
   1. Misfolding (antioxidants, small molecules)
   2. Spread (immunotherapy)
   3. Microbiome modifications

3. These therapies have shown promise in animal models

4. Being safe in Phase I studies

5. Currently many are on Phase II, several at UCSD
Thank you!

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