Critical Path for Parkinson’s: Collaboration to Enable Patient Focused Drug Development and Precision Medicine

Diane Stephenson, PhD, Executive Director, Critical Path Institute

April 27, 2018
A little about me sets the stage for today…..

Pharma was taking too long…

Diane, the Executive Director Critical Path for Parkinson’s, shares why she left job at the largest pharmaceutical company in the world to create better, faster ways to develop new treatments.

I left my job at the largest pharmaceutical company in the world because I knew that it was taking too long to bring new treatments to people like my brother. I needed to find another way to bring hope to my family. So, I joined the Critical Path Institute, a non-profit organization based in Arizona, which exists to make it faster, cheaper and more efficient to get new therapies to patients.
What is the Critical Path Institute?

A trusted, neutral third party delivering new methods and tools for clinical trials which benefit the whole community.
Critical Path for Parkinson’s Consortium – Accelerating therapies for PD

Academic Experts

Individual Advisors

Patient-Advocacy Organizations
- Parkinson’s Disease Foundation
- Michael J. Fox Foundation
- Davis Phinney Foundation
- The Cure Parkinson’s Trust

UK Academic Institutions
- University of Oxford
- University of Cambridge
- Newcastle University
- University of Glasgow

People with Parkinson’s

NIH

AbbVie

Pfizer

Merck

UCB

Lundbeck

Biogen

GE Healthcare

Patient-Advocacy Organizations

UK Academic Institutions
‘Pre-competitive’ collaboration

Working together to solve these problems and create tools that will benefit the whole community.
New Parkinson’s Disease treatments are urgently needed

- There is no cure for Parkinson's disease
- Current medications only help control the symptoms
- None stop the progression of the disease
- In some cases, surgery called Deep Brain Stimulation may help with tremor and rigidity
- Medications have not changed much over the last 25 years
- There is a need for new drug therapies, especially for the non-motor symptoms

https://www.researchgate.net/publication/282812862_New_insight_into_the_therapeutic_role_of_the_serotonergic_system_in_Parkinson%27s_disease/figures?lo=1
Many new promising new therapies are in the pipeline

“A better appreciation of regulatory pathways and requirements by scientists, clinical Investigators, and the pharamaceutical industry will likely help reduce the Cost and time of Drug Development, and speed the approval process”
Parkinson’s Disease Pathophysiology

--so many targets for intervention

http://physrev.physiology.org/content/91/4/1161
Nonclinical Models for Drug Discovery/Development---yet none truly represent true Parkinson’s disease

- Cellular Models
- Primate Models
- Rodent Models
Parkinson’s disease symptoms are widespread and disabling

From: Poewe et al., Nature Revs vol 3, no 17013; 1-21, 2017

Each person with Parkinson's will experience symptoms differently
Parkinson’s Disease Drug Development is aiming for disease modification and early intervention

- Large, global, clinical and observational datasets are available
- Increased understanding of disease progression and sub-clinical syndromes
- Emerging biomarkers, genes and available technologies and biospecimens
Patients’ Voice on the Need for Early Treatment

• Parkinson’s UK 2013-14 survey of patient’s needs from research highlighted strong needs for BOTH new symptomatic treatment AND stopping/slowing progression

STOPPING PROGRESSION AT AN EARLY STAGE was the strongest desire of persons with Parkinson’s.

This will only be possible through successful trials in early stage patients.

http://parkinsonsed.com/pd-dialogues/early-stage-parkinsons
Sept 22, 2015
The FDA held a public meeting on patient focused drug development for Parkinson’s and Huntington’s diseases
The 2015 PFDD meeting was their best attended meeting with 45 PD patients attending in person, 10 PD patients attending virtually, 10 FDA regulators were there in person, over 160 people joined by phone to listen to the meeting and 29 comments were made on the public docket following the meeting.
TOPIC 1: Disease Symptoms and Daily Impacts that Matter most to patients

- Motor symptoms
  - “I was unable to type or use a computer mouse with my right hand and unable to use my right foot and leg to drive (following diagnosis)”

- Cognitive impairment
  - “I often go from task to task without ever completing anything”

- Sleep disturbances
  - “lack of sleep caused my right arm to tremor all night”

- Other symptoms
  - GI disturbances, orthostatic hypertension, weight loss, restless leg, swallowing difficulties, pain, sweating, speech problems

- Reliance on others
  - “I fear the people I love most in the world will have to take care of me”

- Ability to perform at work

- Isolation and impact on relationships
Why do drugs fail to reach people in need?

- Poor drug candidate
- Wrong target
- Inadequate efficacy
- Wrong patient population
- Inadequate efficacy
- Wrong Dose
- Toxicity in select patients
New approaches are needed to tackling drug development challenges

Traditional Drug Development Approach

Reliance on limited information and experience based on:
- A small set of KOLs
- Small, possibly outdated, datasets
- Last paper bias

Data and Quantitative Model Based Drug Development Approach

A modern approach based on:
- Integrated global datasets including relevant populations and endpoints
- Quantitative models of disease progression, patient population and endpoint behavior
What could we do if we had all the data from Parkinson’s studies in one place?

Data from clinical trials and cohorts → Standardization and integration → Researchers, Regulators, Industry

CDISC Data Standards
C-Path Data Mapping and Integration Process
Critical Path for Parkinson’s Worldwide Database

CPP v3.0 Integrated Parkinson’s Database Available to Members

Heinzel et al., JPD 7(3):423-432, 2017

PPMI (n=1223)
CamPaIGN (n=142)
OPDC Discovery Cohort (n=877)
ICICLE (n=314)
Tracking Parkinson’s (n=1998)
PRECEPT (n=806)

TOTAL NUMBER OF SUBJECTS: 5360
We can learn from past clinical trials

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>GPI-1485</td>
<td>Neuritominophilin</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Glutamate antagonist</td>
</tr>
<tr>
<td>CEP-1347</td>
<td>Anti-apoptotic</td>
</tr>
<tr>
<td>Paliroden</td>
<td>Stimulates NGF</td>
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<tr>
<td>Co Q10</td>
<td>Mitochondrial enhancer</td>
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<tr>
<td>Pramipexole</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>Cogane</td>
<td>Modulates GDNF &amp; BDNF</td>
</tr>
<tr>
<td>Creatine</td>
<td>Mitochondrial modulator</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>PPAR-γ agonist; anti-inflammatory</td>
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<tr>
<td>Rasagiline</td>
<td>MAO-B inhibitor</td>
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<tr>
<td>Glutathione</td>
<td>Antioxidant</td>
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<tr>
<td>Mitoquinone</td>
<td>Mitochondrial enhancer</td>
</tr>
<tr>
<td>TCH346</td>
<td>Propargylamine</td>
</tr>
</tbody>
</table>
Future model of Parkinson’s therapies

Parkinson’s - Not all one flavor

Personalized Medicine targeted treatments

As modified from Alberto Espay
Up to 15% of people with early Parkinson’s who take part in trials may not have the condition at all

Beth Vernaleo, Parkinson’s Disease Foundation
Some people worsen fast, others slowly...

- **Early stage**: Slow worsening
- **Late stage**: Fast worsening

Time

Worsening
Using imaging to predict the future

Worsening

Late stage

Early stage

Time

Fast worsening

Slow worsening
Using imaging as a biomarker in trials endorsed by EMA

Normal brain scan (no dopamine deficiency)

Dopamine deficiency consistent with Parkinson’s

The Parkinson’s disease imaging biomarker is the first biomarker to be qualified by Regulatory Authorities
What impact could this make?

Using biomarkers to recruit the right people to trials increases chances of drug approvals.

Amplion/BIO report, 2016
Critical Path for Parkinson’s is already changing the landscape

Selecting more appropriate subjects for clinical trials will reduce the numbers needed and make trials more efficient.
The Critical Path for Parkinson’s Consortium brings together the pharmaceutical industry, academic institutions, regulatory agencies, and patient organizations from around the world to shape the future of innovative clinical trials for people with Parkinson's.

World Parkinson's Day 2018
CPP in collaboration with Parkinson's UK

Integrate even more data from around the world to help create tools that bring:
Can Computerized Modeling Help?

Model Informed Drug Development

- Using computerized models to simulate different ‘what if’ scenarios aimed at identifying the **right drug, right patient at the right time**

**Input**

- **Studies**
  - CamPaiGN
  - OPDC
  - PPMI
  - PRECEPT
  - Tracking PD
  - ICICLE
  - ADAGIO
  - DATATOP

**Disease Model**

- UPDRS II and III at baseline
- Sex
- Age
- Candidate genes genotype
- Disease duration
- Lost to follow-up
- Concomitant PD medication
- Longitudinal UPDRS II and III
- Dopamine transporter imaging
- Hoehn and Yahr stage at baseline

**Output**

- Understanding of motor worsening
- Trajectory
- Rate
- Predictors

*UPDRS = Unified Parkinson’s Disease Rating Scale; PD = Parkinson disease*
The future: a trial ‘flight simulator’?

- How many participants?
- What type?
- What shall we measure?
- What dose?
- How long for?
This has been achieved for Alzheimer’s disease: other diseases are waiting

“Model-based drug development was one of the goals defined in FDA’s 2004 Critical Path Initiative report, and this new tool sets the stage for applying new technologies to accelerating medical product development,” Janet Woodcock, FDA
The landscape of digital health promises transformation
The landscape of digital health promises transformation
Summary

• Parkinson’s disease therapies are challenging to develop. Critical Path for Parkinson’s is a multinational collaboration set in place to tackle the challenges together
• CPP has created the largest fully curated integrated database for Parkinson’s (currently includes data from >5000 patients)
• EMA is poised to qualify the first ever imaging biomarker for Parkinson’s. This is being widely used to select the right participants for clinical trial programs currently starting in US and Europe including UK.
• Regulators are incentivized to listen to the voice of the patient to bring meaningful safe and effective therapies to those living with Parkinson’s
• Modeling tools are being developed to simulate clinical trials and increase the chances of success of future drug development programs
• Collaboration around the world is urgently needed to speed the path to effective treatments
Remember:
Non pharmaceutical interventions are important

The Best Medicine? The Influence of Physical Activity and Inactivity on Parkinson’s Disease

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There is a lot of exciting new evidence that indicates that physical exercise is beneficial for PD patients to keep them mobile and can even relieve some of their symptoms. Whether it’s bicycling, yoga, tai chi, swimming or boxing, keeping active is shown to delay and even improve some symptoms

Mov. Disord. 2016 doi:10.10002/mds.26728
Acknowledgements

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