A Path to Accelerating Treatments for Neurodegenerative Diseases

The Coalition Against Major Diseases (CAMD)

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Critical Path Institute
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Modern clinical trials are very, very costly. A collaborative effort is necessary to provide more efficient clinical trials, and for individuals organizations to continue to invest in Alzheimer’s Disease and Parkinson’s Disease research.
Coalition Against Major Diseases: Tools to Advance Effective Treatments for Alzheimer’s and Parkinson’s Disease

Government/Regulatory participants:
- European Medicines Agency
- FDA
- National Institute on Aging

Non-profit research members:
- Alliance for Aging Research
- Alzheimer’s Association
- CAFA
- US Against Alzheimer’s

Industry members:
- AstraZeneca
- GE Healthcare
- MSD
- Meso Scale Discovery
- Boehringer Ingelheim
- GlaxoSmithKline
- Novartis
- Orion
- Bristol-Myers Squibb
- Innogenetics
- Johnson & Johnson
- Pfizer
- Lilly
- Roche
- Genentech
- Sanofi
- TEVA
- Eisai
- Merck
- Forest Laboratories, Inc.

Nonmember participants: Academic key opinion leaders, CROs
<table>
<thead>
<tr>
<th>Consortia</th>
<th>Focus Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coalition Against Major Diseases</td>
<td>UNDERSTANDING DISEASES OF THE BRAIN</td>
</tr>
<tr>
<td>Critical Path to TB Drug Regimens</td>
<td>TESTING DRUG COMBINATIONS</td>
</tr>
<tr>
<td>Multiple Sclerosis Outcome Assessments</td>
<td>DRUG EFFECTIVENESS IN MS</td>
</tr>
<tr>
<td>Polycystic Kidney Disease Consortium</td>
<td>NEW IMAGING BIOMARKERS</td>
</tr>
<tr>
<td>Patient-Reported Outcome Consortium</td>
<td>DRUG EFFECTIVENESS</td>
</tr>
<tr>
<td>Electronic Patient-Reported Outcome</td>
<td>DRUG EFFECTIVENESS</td>
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<tr>
<td>Predictive Safety Testing Consortium</td>
<td>DRUG SAFETY</td>
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Seven global consortia collaborating with 1,000+ scientists and 41 companies

- Biomarkers
- Clinical Outcome Assessment Instruments
- Clinical Trial Simulation Tools
- Data Standards
The mission of CAMD is to advance innovative drug development tools through a regulatory path that accelerates therapies for neurodegenerative diseases.

Firsts:
- Therapeutic Area clinical data standards published by CDISC (AD and PD)
- Unified CDISC database of Alzheimer’s disease clinical trial information provided by multiple pharmaceutical companies
- Neuroimaging biomarker for Alzheimer’s Disease qualified by a regulatory agency (EMA)
- Clinical trial modeling and simulation tool to achieve a regulatory endorsement
“For an industry that requires a long-term view of research and development, recognizing the value of predictive tools would seem to be a no-brainer.”
Modeling and Simulation as a Tool to Enhance Understanding of Alzheimer’s Disease

INPUTS
- Data
- Clearly Defined Assumptions
- Ideas & Scientific Knowledge

MODELING
Integrated, mathematical representation of all inputs

OUTPUTS
- Portable, integrated form of knowledge
- Exploration of Knowledge Gaps
- Enhanced Understanding
- Predictions vs. Observations
- Test idea concepts

Enhanced Decision Making
Value of Data Sharing, Standards and Pooling: CAMD experience

- Nine member companies agreed to share data from 22 trials
- The data were not in a common format
- The data needed to be combined in a consistent manner
- All data were remapped to the CDISC Alzheimer’s Disease standard and pooled

A new *in silico* modeling tool was created through the application of data standards and was recently endorsed by the FDA and EMA
Parkinson’s Disease:
Time for Innovation is Long Overdue

TODAY’S BEST PARKINSON’S DRUG WAS DISCOVERED IN 1967

LYNDON B. JOHNSON WAS PRESIDENT AND NEIL ARMSTRONG HAD NOT YET WALKED ON THE MOON.

www.michaeljfox.org

Courtesy of:
Michael J Fox Foundation
Parkinson’s Disease: The Unmet Need

Second most common neurodegenerative disorder

6 million patients worldwide

Prevalence to double by 2030

Direct and indirect burden of PD in the US: $10-30MM annually

1 new patient diagnosed in the US every 9 minutes

Dorsey et al. 2007

Figure 2. Projected growth rates in number of individuals over 50 with Parkinson disease in the most populous nations in Western Europe and the world from 2005 to 2030.
Progression of Parkinson’s Disease

- Synuclein aggregation; autonomic, olfactory, sleep dysfunction and restless leg syndrome in some.
- Dopaminergic neuron dysfunction and death with synuclein deposits in Lewy bodies.
- Cognitive decline with cortical Lewy bodies.
- Gait and balance disorder as affects pontine nuclei.

M. Schlossmacher
Pathophysiology and Mechanisms Underlying PD

Cut section of the midbrain where a portion of the substantia nigra is visible.

Substantia nigra as seen in Parkinson's disease.

Lewy Bodies (α-Synuclein)

Molecular Genetic Neuropathology of Parkinson's Diseases
An Evolving Concept of Neurodegenerative Movement Disorders

α-synuclein pathology

Sporadic SNCA & GBA mutations

Mutations in: DJ1, PINK1

 Parkinson

LRRK2

FTDP-17 PSP CBD AD LBD

PD PDD DLB

From Foreman et al., 2006

α-Syn in salivary gland

Courtesy of T. Beach
Parkinson’s Disease: The Challenge Shared with AD

Slow progressive neurodegeneration affecting multiple domains, with increasing burden over time

  Long prodromal period that precedes symptom onset

Symptomatic therapies available with decreasing efficacy over disease course

Insensitive outcome measures often impacted by factors other than treatment effect

High clinical failure rate for novel therapeutics

Clinical trials required to demonstrate efficacy, especially disease modification, are long and costly

  Trial outcomes and methods often confound symptomatic and disease modifying effects
Parkinson’s Disease: Current Efforts

Extensive efforts to gain insight into disease progression and predictive and progression biomarkers

Recognition, and characterization, of non-motor aspects of PD

Multiple symptomatic and disease modifying therapies currently in development

No currently accepted biomarker or clinical trial design that can be reliably used to identify disease modification

We can’t continue to use the same clinical methods, trial designs and outcome measures and expect to see different results.
Discovery of potential disease modifying therapies is scientifically challenging, requiring novel science and innovative thinking.

Clinical development of the next generation of novel therapeutics is no less challenging.

Quantitative PD progression and clinical trial models are under development providing:

- Application of prior experience
- Simulation of potential trial designs (patient selection, trial size/duration)
- Improved understanding of the effect of drop-outs and placebo response

Opportunity remains to expand and further validate a PD disease model including quantification of biomarker-outcome relationships.

Holford and Nutt, 2011

Lee and Gobburu, 2011
Parkinson’s Disease: What is Needed for Success?

- Precompetitive data sharing
  - Universal informed consent
- Applying new technologies and innovation
- Novel discoveries for new targets and biomarkers (genetics and environmental etiologies)
- Resources
- Creative minds and talent - That’s You!
Most Promising Biomarkers for CNS Diseases
CAMD’s Initiatives in Parkinson’s Disease

- PD clinical data standards
- PD C-Path online data repository
- PD imaging biomarker qualification team
- PD quantitative disease progression modeling
- Educational awareness...precompetitive data sharing in PD
Acknowledgements
CAMD PD team members

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Regan Fong, Chao Chen (GSK)
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Yafit Stark (Teva)
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Karl Kieburtz, Charles Venuto (Univ Rochester)

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Back up slides
CAMD AD Modeling Team  
**Journey to Success**

**AD Trial Simulation Tool Receives Regulators’ Blessings**

**AD Modeling Team Members:**

- Klaus Romero
- Brian Corrigan
- Kaori Ito
- Jim Rogers
- Dan Polhamus
- Richard Meibach
- Richard Mohs
- Yaakov Stern
- Lon Schneider
- Gary Cutter
- Yaning Wang
- Vikram Sinha
- Li Zhang
- Marc Walton
- Nick Kozauer
- Issam Zineh
- Maria Isaac
- David Brown
- Jean Georges
- Spiros Vamvakas
- Robert Hemmings
- Luca Pani

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**Submission for Regulatory Evaluation**

- **NOVEMBER 3, 2009**
  - CAMD Coordinating Committee Meeting
- **DECEMBER 21, 2009**
  - FDA Letter of Intent
- **DECEMBER 23, 2009**
  - Cover letter and Briefing Booklet to FDA
- **APRIL 22, 2010**
  - FDA Written feedback
- **APRIL 28, 2010**
  - Meeting with CDER Alzheimer’s Disease Modeling Review Team
- **NOVEMBER 22, 2011**
  - Submission to FDA
  - Comments received from FDA
- **MARCH 27, 2012**
  - Responses to FDA submitted
- **AUGUST 22, 2012**
  - Detailed discussion with FDA regarding the programming code
- **JANUARY 7, 2013**
  - AD trial simulation tool deemed fit for purpose as a drug development tool
- **JUNE 12, 2013**
  - AD trial simulation tool qualified for use in trial design
After recent AD Phase III failures… What’s next?

Reasons for Phase III Submission Failures: 2007-2010

- Efficacy: 66%
- Safety: 21%
- Financial: 7%
- Not disclosed: 6%

The Solution:

Collaborations

that enable ......

- Sharing knowledge
- Learning from failures
- Public-Private Partnerships
## Movement Disorders

<table>
<thead>
<tr>
<th>Healthy subject</th>
<th>Parkinson’s MRI/SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement disorders without striatal dopaminergic deficit (separable by SPECT)</td>
<td>Movement disorders with striatal dopaminergic deficit (inseparable by SPECT)</td>
</tr>
<tr>
<td>Vascular PS</td>
<td>Corticobasilar Degeneration</td>
</tr>
<tr>
<td>Drug induced</td>
<td>Multiple System Atrophy</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Lewy Body Dementia</td>
</tr>
<tr>
<td>Essential Tremor</td>
<td>Progressive Supranuclear Palsy</td>
</tr>
<tr>
<td>Idiopathic Dystonia</td>
<td>Rare genetic motor disease</td>
</tr>
<tr>
<td>Atypical tremors</td>
<td>Toxin-induced parkinsonism</td>
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<tr>
<td>Alzheimer’s disease</td>
<td>Post-encephalitic parkinsonism</td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>Huntington’s disease</td>
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<tr>
<td>Wilson’s Disease</td>
<td>Post traumatic encephalopathy</td>
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PD Imaging Biomarker for Patient Enrichment

Imaging of Dopamine Transporter (DAT)

SWEDDS = scans without evidence of dopamine deficiency

% SWEDDS in PD trials

PD trials
ELLDOPA: L-dopa
PRECEPT: MLK inhibitor
CEP1347
REAL: ropinirole
CALM: pramipexole
GPI1485: immunophilin