Parkinson’s Progression Markers Initiative (PPMI)

John Q. Trojanowski, M.D., Ph.D.

Parkinson’s Progression Marker Initiative
NINDS Udall Center of Excellence For Parkinson’s Disease Research,
NIA Alzheimer’s Disease Core Center,
Center for Neurodegenerative Disease Research,
Marin S. Ware Alzheimer Program, Institute on Aging,
Perelman School of Medicine at the University of Pennsylvania,
Department of Pathology and Laboratory Medicine,
University of Pennsylvania, Philadelphia, PA
PPMI - a $50MM study funded by the Michael J. Fox Foundation and others- began in June, 2010 - seeks to develop PD progression markers

Rationale:

• Disease modifying PD therapeutics remain a major unmet need
• A major obstacle to PD clinical trials is the lack of biomarkers for
  – Disease mechanism
  – Drug mechanism
  – Dosage determination
  – Study eligibility
  – Stratification into PD sub-types
  – Correlation with clinical signals
• Biomarkers would potentially shorten study duration, reduce study sample size, limit study costs
# PPMI Study Details: Synopsis

## Study population
- 400 de novo PD subjects (newly diagnosed and unmedicated)
- 200 age-and gender-matched healthy controls
- ~70-80 SWEDD subjects
- Subjects followed for a minimum of 3 years and maximum of 5 years

## Assessments/ Clinical data collection
- Motor assessments
- Neuropsychiatric/neurobehavioral testing
- Olfaction
- DaTSCAN imaging, MRI

## Biologic collection
- DNA collected at screening
- Serum, whole blood and plasma collected at each visit; urine annually
- CSF collected at baseline, 6mo 12 mo and then annually
- Samples aliquotted and stored in central biorepository

## Initial verification studies
- Lead biologic candidates to be tested:
  - Alpha-synuclein (CSF)
  - DJ-1 (CSF and blood)
  - Urate (blood)
  - Abeta 1-42 (CSF)
  - Total tau, Phospho-tau (p-181) (CSF)

## PD treatment
- De novo for ~6 months
- Can participate in clinical trials (including interventional trials) after 12 months
Natural History of Parkinson’s Disease

Pre-diagnostic

Symptomatic Diagnosis

PPMI

Neuron Function

Time

Clinical Ratings
# PPMI Steering Committee and Cores

<table>
<thead>
<tr>
<th>Steering Committee</th>
<th>PI-K Marek, A Siderowf, C Scherzer, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, C Tanner, B Ravina (core leaders, MJFF, ISAB)</th>
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</thead>
</table>
| Clinical Coordination Core | University of Rochester’s Clinical Trials Coordination Center  
- PI: Alice Rudolph |
| Imaging Core | Institute for Neurodegenerative Disorders  
- PI: John Seibyl |
| Statistics Core | University of Iowa  
- PI: Chris Coffey |
| Bioinformatics Core | Laboratory of Neuroimaging (LONI) at UCLA  
- PI: Arthur Toga |
| BioRepository | Coriell/BioRep  
- PI: Alison Ansbach, Pasquale De Blasio, Michele Piovella |
| Bioanalytics Core | University of Pennsylvania  
- PI: John Trojanowski, Les Shaw |
| Genetics Core | National Institute on Aging/NIH  
- PI: Andy Singleton |
PPMI Clinical Sites
## Schedule of Events - PD

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Hollywood star leads the way in Parkinson’s research

The Michael J Fox Foundation is after the holy grail in Parkinson’s research—disease-modifying treatments. They have launched Fox Trial Finder, which aims to get more patients involved in clinical trials, and are on the hunt for therapeutic biomarkers. Dara Mohammadi reports.
Screening for impulse control symptoms in patients with de novo Parkinson disease
A case-control study

ABSTRACT

Objective: To determine the frequency and correlates of impulse control and related behavior symptoms in patients with de novo, untreated Parkinson disease (PD) and healthy controls (HCs).

Methods: The Parkinson’s Progression Markers Initiative is an international, multisite, case-control clinical study conducted at 21 academic movement disorders centers. Participants were recently diagnosed, untreated PD patients (n = 168) and HCs (n = 143). The outcome measures were presence of current impulse control and related behavior symptoms based on recommended cutoff points for the Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease (QUIP)-Short Form.

Results: There were 311 participants with complete QUIP data. Frequencies of impulse control and related behavior symptoms for patients with PD vs HCs were as follows: gambling (1.2% vs 0.7%), buying (3.0% vs 2.1%), sexual behavior (4.2% vs 3.5%), eating (7.1% vs 10.5%), punding (4.8% vs 2.1%), hobbyism (5.4% vs 11.9%), walkabout (0.6% vs 0.7%), and any impulse control or related behavior (18.5% vs 20.3%). In multivariable models, a diagnosis of PD was not associated with symptoms of any impulse control or related behavior (p ≥ 0.10 in all cases).

Conclusions: PD itself does not seem to confer an increased risk for development of impulse control or related behavior symptoms, which further reinforces the reported association between PD medications and impulse control disorders in PD. Given that approximately 20% of patients with newly diagnosed PD report some impulse control or related behavior symptoms, long-term follow-up is needed to determine whether such patients are at increased risk for impulse control disorder development once PD medications are initiated. Neurology® 2013;80:176-180
First Chemical Biomarker Study – We Are On Our Way!

Association of cerebrospinal fluid $\text{A}\beta_{1-42}$, t-tau, $\text{p-tau}_{181}$ and $\alpha$-synuclein levels with clinical features of early drug naïve Parkinson’s disease patients

J-H Kang, DJ Irwin, AS Chen-Plotkin, A Siderowf, C Caspell, CS Coffey, T Waligórska, P Taylor, S Pan, M Frasier, K Marek, K Kieburtz, D Jennings, T Simuni, CM Tanner, A Singleton, AW Toga, S Chowdhury, B Mollenhauer, JQ Trojanowski, LM Shaw, & the Parkinson’s Progression Marker Initiative


**Objective:** Evaluate baseline characteristics and relationship to clinical features of CSF $\text{A}\beta_{1-42}$, t-tau, $\text{p-tau}_{181}$ and $\alpha$-syn in PD patients and matched healthy controls (HC) enrolled in PPMI.

**Methods:** CSF biomarkers were measured by xMAP-Luminex platform and ELISA in HC (N=39) and PD (N=63).
Figure 1

<table>
<thead>
<tr>
<th>Total subjects</th>
<th>CSF Hgb&lt;500 ng/ml</th>
<th>CSF Hgb&lt;200 ng/ml</th>
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</table>

Figure 2

Red dot = subject with CSF tau and A profile
Association of cerebrospinal fluid $\text{A}\beta_{1-42}$, t-tau, p-tau$_{181}$ and $\alpha$-synuclein levels with clinical features of early drug naïve PD patients

J-H Kang, DJ Irwin, AS Chen-Plotkin, A Siderowf, C Caspell, CS Coffey, T Waligórsk, P Taylor, S Pan, M Frasier, K Marek, K Kieburtz, D Jennings, T Simuni, CM Tanner, A Singleton, AW Toga, S Chowdhury, B Mollenhauer, JQ Trojanowski, LM Shaw, & the Parkinson’s Progression Marker Initiative*

*JAMA Neurology, In press, 2013

SUMMARY AND CONCLUSIONS

1) Significantly lower concentrations of all measured CSF biomarkers and t-tau/$\text{A}\beta_{1-42}$ ratio in PD compared to HC.

2) Lower CSF $\text{A}\beta_{1-42}$ associated with PIGD which shows a more rapid cognitive decline and poor prognosis compared to tremor-dominant PD patients.

3) CSF $\text{A}\beta_{1-42}$, t-tau, p-tau$_{181}$ and $\alpha$-syn have value for diagnosis and assessment of disease progression in early-stage PD.
α-Synuclein, Tau & Aβ Levels in PPMI & ADNI

MCI progression to AD

Temporal Ordering Of AD Biomarkers Suggests Success In Delineating A Biomarker Profile For PD That Reflects Progression Of PD In PPMI
Acknowledgements: Les Shaw and the Penn PPMI Biomarker Core members Magda Brylska and Mike Figurski, our PPMI study participants, and the amazing PPMI Team!
PPMI Funding Partners

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