Learnings from Parkinson’s disease: Critical role of Biomarkers in successful drug development

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Coalition Against Major Diseases and FDA
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Disclosure

• Co-founder on Molecular Neuroimaging LLC – PET and SPECT imaging services
• Consultant – BMS, GEHC, Lilly, Merck, Navidea, Piramal Pfizer, Sanofi, LTI
PD - Major Challenges

• Progression in inevitable – Motor and non-motor disease features

• Heterogeneity is a hallmark of disease – Subsets of PD with likely different etiology, disease course, response to therapy

• Degeneration begins long before symptoms arise - Where does PD begin, when does PD begin, how does PD progress during the pre-diagnostic period
WHY BIOMARKERS

- Disease Mechanism
- Drug Mechanism/Drug dosage
- Improve diagnostic accuracy (enrich a study population)
- Identify subsets that might develop clinical outcomes
- Identify subsets that might respond to therapy
- Repeated measure to assess progression
- Eliminate confounding of symptomatic therapy
- Evaluate efficacy of disease modifying therapeutic
- Reduced sample size and more rapid assessment of effect - reduce cost and improve efficiency of clinical studies
- Assist in regulatory approvals
- Measurement prior to onset of symptoms
- Used to correlate clinical, imaging, genetic and biofluid biomarkers
- Provide objective quantitative outcomes at multiple clinical sites
Natural History of PD

Neuron Function

Prodromal

Symptomatic

Diagnosis

Time

Clinical Ratings
Natural History of PD

Symptomatic

Prodromal

Neuron Function

Clinical Ratings

DA Degen

DA Degen PD range

Early clinical markers

Motor symptoms

Diagnosis

Rx with DA

Motor fluctuations

ADLS, Work effected

Cognition

Gait/balance

Severe Disability

-15yr -2yr -1yr 0 1-2yr 5yr 10yr 15yr
PD Biomarker Candidates

**CLINICAL MARKERS**

- Cognition
- Behavioral
  - Depression
  - Apathy
  - Anxiety
  - ICD
- Autonomic
  - Constipation
  - Bladder
  - Sexual
  - Cardiac
- Olfaction
- Sleep- RBD
- Skin
- Motor Analysis
- Speech

**IMAGING - PHENOTOMICS**

- DA-SPECT/PET. Synuclein,
- MRI –DTI/RS, volumetrics
- Nigral Ultrasound

**BIOLOGICS**

- Blood, CSF, Urine
- Alpha-synuclein, DJ1, Urate, Tau, Beta-Amyloid, ApoA1,

‘OMICS’

- RNA Profiling
- DNA exome sequencing

**GENETICS**

- Synuclein, LRRK2, GBA, Parkin, DJ-1, Pink 1, Tau
Pre-synaptic Dopaminergic Imaging

*Nigral Dopamine loss - Face validity*

Reduction in early PD 50% Put

Reduction Put>Caud

Reduction asymmetric

Correlation with severity (UPDRS)

Reduction in Prodromal

Monitor PD progression

123I β-CIT-DAT

18F AV-133-VMAT2

18F-DOPA-AADC

Healthy +Parkinson disease
Baseline PRECEPT -
% Age expected Putamen
[123I] β-CIT uptake

Subject Number

% of age expected Putamen [123I] β-CIT uptake

DAT Deficit

Scans without evidence of dopaminergic deficit
SWEDD
PRECEPT study - FOLLOWUP IMAGING AND CLINICAL OUTCOMES BY SWEDD STATUS AT BASELINE

<table>
<thead>
<tr>
<th>% Change $[^{123}\text{I}]\beta$-CIT</th>
<th>SWEDD &gt;80%</th>
<th>DAT Deficit &lt;=80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum:</td>
<td>-0.2 (12.2)</td>
<td>-8.5 (11.9) *</td>
</tr>
<tr>
<td>Caudate:</td>
<td>1.0 (13.1)</td>
<td>-6.1 (12.5) *</td>
</tr>
<tr>
<td>Putamen:</td>
<td>-1.9 (12.2)</td>
<td>-13.1 (15.1) *</td>
</tr>
<tr>
<td>CLINICAL</td>
<td>N = 91</td>
<td>N = 708</td>
</tr>
<tr>
<td>Change in Total UPDRS</td>
<td>0.5 (6.9)</td>
<td>10.5 (8.9) *</td>
</tr>
<tr>
<td>Change in Motor UPDRS</td>
<td>-0.4 (5.0)</td>
<td>7.0 (6.9) *</td>
</tr>
<tr>
<td>Need for DA treatment at 12 mo</td>
<td>16.7% (CI 10.2, 26.6)</td>
<td>50.9% (CI 47.2, 54.8) *</td>
</tr>
</tbody>
</table>

Mean (SD) for Change in $[^{123}\text{I}]\beta$-CIT and UPDRS, Percent (CI) for need for DA treatment. * indicates p < 0.01
## PRECEPT Dx at Termination

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>SWEDD Subjects</th>
<th>DAT DEFICIT Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAT Deficit Parkinsonism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confident PD</td>
<td>40 (44%)</td>
<td>609 (86%)</td>
</tr>
<tr>
<td>PD + Another</td>
<td>2 (2%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>PSP</td>
<td>0 (0%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Corticobasal Degeneration</td>
<td>1 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Lewy Body Disease</td>
<td>2 (2%)</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Multiple System Atrophy</td>
<td>4 (4%)</td>
<td>37 (5%)</td>
</tr>
<tr>
<td>Hemiparkinson Syndrome</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Juvenile Parkinsonism</td>
<td>1 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50 (55%)</td>
<td>681 (96%)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>DIAGNOSIS</th>
<th>SWEDD Subjects</th>
<th>DAT DEFICIT Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudo-Parkinsonism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential Tremor</td>
<td>15 (17%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Dopa-Responsive Dystonia</td>
<td>1 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Alzheimers</td>
<td>0 (0%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Normal Pressure Hydrocephalus</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Psychogenic Illness</td>
<td>3 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Vascular Parkinsonism</td>
<td>5 (6%)</td>
<td>13 (2%)</td>
</tr>
<tr>
<td>Other Neurological</td>
<td>5 (6%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>No PD or Neurological</td>
<td>9 (10%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>40 (45%)</td>
<td>26 (4%)</td>
</tr>
</tbody>
</table>

Diagnoses of 707 DAT deficit and 90 SWEDD subjects by PRECEPT site investigators unaware of imaging data at termination (approx 21 month f/u)
PRECEPT SWEDD 6 yr follow-

PRECEPT study – Follow up at 72 months

SWEDD N=42,
% Ann Change from Baseline - 1.2%

DAT Deficit N=374,
% Ann Change from Baseline - 5.1%
Natural History of PD

Prodromal

Symptomatic

Diagnosis

Time

Neuron Function

Clinical Ratings
RBD and Risk of PD

• Risk of PD in patients with idiopathic RBD is about 5%/yr
• Increased risk extends for 10-20 years from RBD diagnosis

From Postuma, Neurology 2009
Decreased striatal dopamine transporters uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eyemovement sleep behaviour disorder: a prospective study
A. Iranzo, F Lomeña, H Stockner, F Valdeoriola, I Vilaseca, M Salamero, JL Molinuevo, M Serradell, J Duch, J Pavía, J Gallego, K Seppi, B Högl, E Tolosa, Werner Poewe, J Santamaria, for the Sleep Innsbruck Barcelona (SINBAR) group
Lancet, 2010

17 of 43 RBD subjects demonstrate reduced DAT uptake

<table>
<thead>
<tr>
<th></th>
<th>Participants with RBD (n=43)</th>
<th>Controls (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left putamen:occipital</td>
<td>2.46 (0.30)</td>
<td>2.68 (0.15)</td>
<td>0.007</td>
</tr>
<tr>
<td>Right putamen:occipital</td>
<td>2.42 (0.30)</td>
<td>2.62 (0.18)</td>
<td>0.012</td>
</tr>
<tr>
<td>Left caudate:occipital</td>
<td>2.98 (0.37)</td>
<td>3.17 (0.28)</td>
<td>0.057</td>
</tr>
<tr>
<td>Right caudate:occipital</td>
<td>3.01 (0.38)</td>
<td>3.30 (0.32)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated. RBD = Idiopathic rapid-eye movement sleep behaviour disorder. 

6/17 developed PD or DLB within 2.5 years
PARS: study scheme
Eligible subjects sent UPSIT’s ($n = 9,379$)
52% returned
Valid UPSIT’s ($n = 4,871$)
(< 15% percentile)
Olfactory loss ($n = 650$)

PHASE 1
First degree relatives, non-relatives

PHASE 2
Clinic visit - 385
1. UPDRS
2. Diagnostic form
3. SCOPA-aut
4. Non-motor review
5. Neuropsych assess

Imaging visit- 303
1. DAT imaging
2. HRV
3. Blood, CSF sampling
### PARS baseline DAT IMAGING -

<table>
<thead>
<tr>
<th>Age expected Putamen DAT density</th>
<th>HYPOSMIC (≤15%) N=203</th>
<th>NORMOSMIC (&gt;15%) N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65% (DAT deficit)</td>
<td>23 11.3%</td>
<td>1 1.0%</td>
</tr>
<tr>
<td>65% - ≤80% (Indeterminate)</td>
<td>35 17.2%</td>
<td>7 7.0%</td>
</tr>
<tr>
<td>&gt;80% (NO DAT deficit)</td>
<td>145 71.5%</td>
<td>92 92.0%</td>
</tr>
</tbody>
</table>

- Hyposmia enriches for DAT deficit (28.5% compared to 8%)
- Severe DAT deficit highly enriches for DAT deficit (11.3% compare to 1%)
Longitudinal PARS

<table>
<thead>
<tr>
<th>Best Current Diagnosis</th>
<th>DAT deficit (&lt;65% age expected uptake) at BL (n=23)</th>
<th>DAT deficit (&lt;65% age expected uptake) at any scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL (n=23)</td>
<td>Yr 2 (n=23)</td>
</tr>
<tr>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-clinical PD</td>
<td>7 (30%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>No neuro dx</td>
<td>10 (43%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>other</td>
<td>6 (26%)</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

Phenoconversion rate is 61% at 4 years for subjects with a severe DAT deficit (<65% of age expected DAT uptake) at baseline.

Progression of DAT deficit among hyposmics increase number of subjects with (<65% of age expected DAT uptake)
Natural History of Parkinson disease

Neuron Function

Pre-diagnostic

Symptomatic

PPMI

Time
# PPMI Study Details: Synopsis

## Study population
- 400 de novo PD subjects (newly diagnosed and unmedicated)
- 200 age- and gender-matched healthy controls
- 70 SWEDD
- 100 Prodromal - Olfactory/RBD/LRRK2
- 500 LRRK2 - PD manifest and non-manifesting family members
- 100 Synuclein - PD manifest and non-manifesting family members
- Subjects will be followed for 3 to 5 years

## Assessments/ Clinical data collection
- Motor assessments
- Neurobehavioral/cognitive testing
- Autonomic, Olfaction, Sleep
- DaTSCAN, AV133, Amyloid, DTI/RS MRI

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

## Data and Biosamples shared on website - www.ppmi-info.org
- >160,000 Data downloads
- > 35 Sample requests via BRC
- Ancillary study development
Comparison of PPMI PD vs SWEDD subjects

- Demographics - PD similar to SWEDD
  - Age, gender, fam hx, disease duration
- Motor assessment - PD > SWEDD at Baseline
  - UPDRS – No progression among SWEDD

- Non-Motor assessment – SWEDD > PD
  - GDS, STAI, Scopa Aut
- Biomarker measure - SWEDD similar to HS
  - Olfaction, CSF synuclein
Conclusion

• Subjects without evidence of DAT deficit do not demonstrate clinical or imaging progression.

• Subjects at risk for PD with DAT deficit have a high incidence of phenoconversion to motor PD.

• PPMI provides an opportunity to examine objective biomarkers in PD and SWEDD subjects and to further assess biomarker progression in prodromal subjects who have DAT deficit.