Natural History of Parkinson disease

Pre-diagnostic

Symptomatic

PPMI

Clinical Ratings

Time

Neuron Function
How to define Prodromal PD

• Enrich a population
• Combine Biomarkers
• Assess biomarker change
• Develop high risk cohort for phenoconversion
### Clinical markers

- **Cognition**
- **Affective**
  - Depression
  - Apathy
  - Anxiety
- **Autonomic**
  - Constipation
  - Bladder
  - Sexual
  - Cardiac
- **Olfaction**
- **Sleep - RBD**
- **Skin**
- **Motor analysis**
- **Speech**

### Biomarkers for PD

- **Imaging – Phenotomics**
  - SPECT/PET-Dopamine - DAT, F-Dopa, VMAT2
  - SPECT/PET-non-dopamine - FDG, MIBG, NE, 5HT, Nicotine, Ach, PBR, Amyloid, â-synuclein
- **MRI-DTI**
- **Functional MRI**
- **Nigral Ultrasound**

- **Genetics**
  - Synuclein, **LRRK2**, GBA
  - Parkin DJ-1, Pink1

- **Laboratory**
  - Synuclein, DJ1, Tau, Amyloid, urate

- **RNA profiling**
- **Metabolomics**
PARS: study scheme
PARS baseline –
Sequential and increasingly intensive biomarker assessment

PHASE 1
First degree relatives, non-relatives

Eligible subjects sent UPSIT’s (n = 9,379)

Valid UPSIT’s (n = 4,871)

52% returned

Valid UPSIT’s (< 15% percentile)

Olfactory loss (n = 650)

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 (&lt;15%) N=203</th>
<th>NORMOSMIC (&gt;15%) N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Percent of cohort</td>
<td>N</td>
</tr>
<tr>
<td>&lt;65% (DAT deficit)</td>
<td>23 11.3%</td>
<td>1 1.0%</td>
</tr>
<tr>
<td>65% - &lt;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>
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- Hyposmia enriches for DAT deficit (28.5% compared to 8%)
- Severe DAT deficit highly enriches for DAT deficit (11.3% compare to 1%)
Factors influencing the risk of DAT deficit (≤ 65% age expected DAT putamen uptake)
Longitudinal PARS - 2 year interval

84% retention – completion in April 2012

6 of 18 <65% DAT - Parkinsonism

7 of 18 <65% DAT Pre- Parkinsonism

None of >65% (n=220) DAT - Parkinsonism
Start with a genetically defined cohort

Initial studies - Asymptomatic LRRK2 carriers
- 4 subjects had reduced DAT during a 4 year period
- 2 of these had abnormal VMAT2
- None had abnormal F-dopa

Possible to detect imaging changes in this pre-motor group
Compensation may occur that differentially effects these imaging outcomes

Longitudinal imaging in a LRRK2 family demonstrates progressive loss of imaging outcomes in unaffected mutation carriers


LRRK2 AJ consortium

LRRK2 15-20% of PD in Askenazi Jewish population
- 3 sites – Tel Aviv, Beth Israel, Columbia, 3 sites in EU

Penetrance uncertain/varied age of onset

Cannot distinguish from IPD

DAT imaging of unaffected carriers to examine pre-diagnostic period.
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
- May be related to RBD severity

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 Valldeoriola, I Vilaseca, M Salamero, JLMolinuevo, 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

Putamen > caudate reduction

6/17 developed PD or DLB within 2.5 years
Proposal to establish pre-motor PPMI cohort defined by DAT deficit

- Utilize existing PPMI infrastructure
  - Sites
  - Cores
  - Database
  - Website
- Utilize LRRK2 cohort
- Utilize Fox Trial Finder
- Utilize existing effort - olfaction, RBD as model
P-PPMI Working group

- Kenneth Marek
- Daniela Berg
- Sohini Chowdhury
- Chris Coffey
- Tom Comery
- Stewart Factor
- Emily Flagg
- Mark Frasier
- Igor Grachev
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- Bernard Ravina
- Andrew Siderowf
- Tanya Simuni
- Todd Sherer
- David Standaert
- Carlie Tanner
- Marcel van der Brug
Proposal to establish pre-motor PPMI cohort define by DAT deficit

- Sequential biomarker strategy to identify DAT deficit cohort – olfaction, RBD, LRRK2
- Focus on subjects with < 65% expected DAT
- Develop a pre-motor risk score
- Follow group with DAT deficit and normal DAT for 2 years (n=100 subjects)
  - Establish pre-motor biomarker signature
  - Define phenoconversion
P-PPMI Outcome measures

- Change in biomarker signature – Clinical, Imaging, biologic
  - Exploratory comparison of P-PPMI to PD Healthy, SWEDD
- Phenoconversion to motor PD
  - How to define phenoconversion – clinical judgement, existing scales
Prodromal biomarker outcomes

- The mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in Prodromal subjects, and where appropriate the comparison of these rates with PD subjects, healthy subjects at study intervals from 3 months to 48 months.

- Correlations between the rates of change in the mean of clinical, imaging and biomic outcomes in prodromal subjects and between PD, SWEDD and healthy subjects at study intervals from 3 months to 48 months.

- Prevalence of measures of clinical, imaging and biomic outcomes in Prodromal subjects at study intervals from baseline to 48 months.
Definition of Phenoconversion

• Clinical Judgement

• Established criteria – GELB, BBB.

• New definition - Adding motor +non-motor symptoms

• Data defined - develop from data

Consensus to utilize robust clinical outcome – ie 2 of 3 cardinal signs of PD +/- asymmetry
P-PPMI Prodromal Recruitment

- Eligibility
  - Combine risk factors to enhance risk of DAT deficit vs
  - Single risk factor to increase number eligible
- From where (cohort dependent)
  - PPMI sites, Fox trial finder, collaborators
- Materials/Media
Eligibility for P-PPMI

- **LRRK2 Relatives**
- **Hyposmic Subjects**
- **RBD subjects**

**DAT imaging**

- **DAT <65% age expected uptake**
  - Enroll in P-PPMI
- **DAT >65% age expected uptake**
  - Excluded from P-PPMI
Eligibility

• > 60 years
• One or more of following
  – hyposmia <15\textsuperscript{th} percentile for age and gender plus one other symptom +
    Constipation (<1 BM/day)
  – RBD – defined by PSG
  – LRRK2 mutation

PLUS
• DAT deficit– Putamen binding ratio <65\% of age expected
Exclusion

- Dementia or other significant neurological disorder
- Tremor
- Current smoker?
- Any clear motor sign of PD
Recruitment Phase
Hyposmic Subjects

Recruitment Sources
- Internet/web-based forms
- Fox Trial Finder
- Location targeted mailings to nurses, veterans
- Family members of clinic patients with PD
Hyposmic Recruitment Schematic

Demographic Form

Centralized Eligibility Review

Eligible

ICF for screening, UPSIT/Other questionnaires (RBD, SRS, BM frequency)

>15th Percentile

<15th Percentile

Ineligible

PPMI Site Referral
Main recruitment source
- Identification of Sleep Center Collaboration at PPMI sites
RBD Recruitment Schematic

Consent to use PSG, Demographic Form

Centralized Review of PSG and Eligibility

Sleep Expert

Eligible

PPMI Site Referral

Ineligible
Recruitment Phase
LRRK2 Subjects/Relatives

- Recruitment sources
  - Internet advertising
  - LRRK2 consortia collaborations
  - Referral by LRRK2 subjects in PD clinics (PPMI sites)
P-PPMI - Assessments

- PPMI PD schedule of activities
- Modify Primary diagnosis
- Phenoconversion – certainty of Dx
- Wish list of other assessments
  - Annual UPSIT
  - HRV
  - Colon biopsy
  - Skin biopsy
  - Blood/CSF analytes
P-PPMI - Providing info to Subjects

- DAT binding
  - DAT deficit uncertain in prodromal PD
  - Include disclosure of DAT in consent
  - Process underway to establish guidelines for disclosure – Karlawish, AD – A4 study
P-PPMI - Implementation

- Amendment
- CRFs
- Develop recruitment forms
- Need for core recruitment
  - Olfaction – demographics and UPSITs
  - RBD – PSG reading
- Process to refer eligible subjects to PPMI sites
P-PPMI - Operations

- Site training
- IRB submission, management
- Recruitment materials
- Forms and CRF development
- Database development
- Imaging Core: Quantitative rapid response process
P-PPMI - Protecting the core PPMI study

- Continued emphasis on recruitment and retention
- Not all sites need participate in P-PPMI or in all aspects – Site Interest Forms
- Focus on Longitudinal PD data
P-PPMI cohort Timeline

• Protocol development Feb – May 2012
• Introduce to PPMI sites – May 2012
• Site IRB approvals – Sept 2012 – Nov 2012
• Budget approvals – Sept 2012 – Nov 2012
• Implement protocol Dec 2012