Disclosure

• Co-founder on Molecular Neuroimaging LLC – PET and SPECT imaging services
• Consultant – BMS, GEHC, Lilly, Merck, Navidea, Piramal
• Pfizer, Sanofi,
Parkinson Progression Marker Initiative

- Disease modifying PD therapeutics remain a major unmet need
- A major obstacle to current phase 2/3 neuroprotection studies is the lack of biomarkers for
  - Disease mechanism
  - Drug mechanism
  - Dosage determination
  - Study eligibility
  - Stratification into PD sub-types
  - Correlation with clinical signals

Requirements for Biomarker Infrastructure

- **Specific Data Set**
  - Appropriate population (early stage PD and controls)
  - Clinical (motor/non-motor) and imaging data
  - Corresponding biologic samples (DNA, blood, CSF)

- **Standardization**
  - Uniform collection of data and samples
  - Uniform storage of data and samples
  - Strict quality control/quality assurance

- **Access/Sharing**
  - Data available to research community → data mining, hypothesis generation & testing
  - Samples available for studies
## PPMI Study 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, VMAT, Amyloid imaging, DTI/RS MRI

### Biologic collection/
- DNA collected at screening
- Serum and plasma collected at each visit; urine collected 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)
PPMI Sites

PPMI SITES IN THE UNITED STATES:
- Arizona PD Consortium (Sun City, AZ)
- Baylor College of Medicine (Houston, TX)
- Boston University (Boston, MA)
- Cleveland Clinic (Cleveland, OH)
- Emory University (Atlanta, GA)
- Institute of Neurodegenerative Disorders (New Haven, CT)
- Johns Hopkins University (Baltimore, MD)
- Northwestern University (Chicago, IL)
- Oregon Health and Science University (Portland, OR)
- The Parkinson's Institute (Sunnyvale, CA)
- PD & Movement Disorders Center at Boca Raton (Boca Raton, FL)
- University of Alabama at Birmingham (Birmingham, AL)
- University of California at San Diego (San Diego, CA)
- University of Cincinnati (Cincinnati, OH)
- University of Pennsylvania (Philadelphia, PA)
- University of Rochester (Rochester, NY)
- University of South Florida (Tampa, FL)
- University of Washington (Seattle, WA)

PPMI SITES IN EUROPE:
- Imperial College (London, UK)
- Innsbruck University (Innsbruck, Austria)
- Paracelsus-Elena Clinic Kassel/University of Marburg (Kassel and Marburg, Germany)
- University of Napoli (Naples, Italy)
- University of Tübingen (Tübingen, Germany)

PPMI SITES IN AUSTRALIA:
- Macquarie University (Sydney, Australia)

Sites to enroll LRRK2 and synuclein subjects will be added.
# PPMI SC and Study Cores

<table>
<thead>
<tr>
<th>Steering Committee</th>
<th>PI-K Marek, C Tanner, T Foroud, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, T Simuni, (core leaders, MJFF, ISAB), S Lasch</th>
</tr>
</thead>
</table>
| Clinical Coordination Core | University of Rochester’s Clinical Trials Coordination Center  
  • PI: Karl Kieburtz, irina Lazurenko, Alice Rudolph, Cindy Casaceli |
| Imaging Core | Institute for Neuropathology and Neuroimaging;  
  • PI: John Seibyl, Norbert Schuff, |
| Statistics Core | University of Iowa  
  • PI: Chris Coffey |
| Bioinformatics Core | Laboratory of Neuroimaging (LONI) at UCLA  
  • PI: Arthur Toga, Karen Crawford |
| BioRepository | Coriell/BioRep  
  • PI: Alison Ansbach, Paola Casalin, |
| Bioanalytics Core | University of Pennsylvania  
  • PI: John Trojanowski, Les Shaw |
| Genetics Core | National Institute on Aging/NIH  
  • PI: Andy Singleton |
| RBD Core | Hephata Hessisches Diakoniezentrum e. V.  
  • PI: Geert Mayer |
| Olfactory Core | Institute for Neurodegenerative Disorders  
  • PI: Danna Jennings |
| Genetics Coordinating Core | Indiana University  
  • PI: Tatiana Foroud |
PPMI is sponsored and partially funded by The Michael J. Fox Foundation for Parkinson’s Research. Other funding partners include a consortium of industry players, non-profit organizations and private individuals.
• **Enrollment** – 419 PD 191 HS 59 SWEDD  **669 subjects**

• **Retention** – 413 PD  183 HS 58 SWEDD - **654 subjects**
## Baseline Demographics and Motor Characteristics

<table>
<thead>
<tr>
<th>Baseline Assessment</th>
<th>PD Subjects (N = 423)</th>
<th>Healthy Controls (N = 196)</th>
<th>SWEDD Subjects (N = 64)</th>
<th>PD p-value relative to HC</th>
<th>PD p-value relative to SWEDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (Range)</td>
<td>61.7 (33 - 85)</td>
<td>60.8 (31 - 84)</td>
<td>60.9 (38 - 79)</td>
<td>0.33</td>
<td>0.58</td>
</tr>
<tr>
<td>Gender (M %/F %)</td>
<td>277 (65%) / 146 (35%)</td>
<td>126 (64%) / 70 (36%)</td>
<td>40 (63%) / 24 (37%)</td>
<td>0.79</td>
<td>0.67</td>
</tr>
<tr>
<td>MDS-UPDRS Mean Score &amp; Sub Scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-UPDRS Total Score</td>
<td>32.3</td>
<td>4.7</td>
<td>29</td>
<td>&lt;0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>MDS-UPDRS Part I</td>
<td>5.5</td>
<td>3</td>
<td>8.7</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MDS-UPDRS Part II</td>
<td>5.9</td>
<td>0.4</td>
<td>5.9</td>
<td>&lt;0.01</td>
<td>0.98</td>
</tr>
<tr>
<td>MDS-UPDRS Part III (Motor Exam)</td>
<td>20.9</td>
<td>1.2</td>
<td>14.3</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr N(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>0 (0%)</td>
<td>184 (97%)</td>
<td>0 (0%)</td>
<td>&lt;0.01</td>
<td>0.7</td>
</tr>
<tr>
<td>Stage 1</td>
<td>179 (43%)</td>
<td>2 (1%)</td>
<td>35 (59%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>229 (56%)</td>
<td>0 (0%)</td>
<td>24 (41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3-5</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Schwab &amp; England (mean)</td>
<td>93.1</td>
<td>NA</td>
<td>94.7</td>
<td>NA</td>
<td>0.05</td>
</tr>
<tr>
<td>First degree family Member with PD (%)</td>
<td>54 (13%)</td>
<td>0 (0%)</td>
<td>14 (24%)</td>
<td>&lt;0.01</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean Duration of Disease (months)</td>
<td>6.6 (0.4 - 35.8)</td>
<td>NA</td>
<td>7.9 (0.5 - 37)</td>
<td>NA</td>
<td>0.16</td>
</tr>
<tr>
<td>Initial Symptoms*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting Tremor</td>
<td>321 (78%)</td>
<td>NA</td>
<td>50 (85%)</td>
<td>NA</td>
<td>0.23</td>
</tr>
<tr>
<td>Rigidity</td>
<td>314 (76%)</td>
<td>NA</td>
<td>33 (56%)</td>
<td>NA</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>339 (82%)</td>
<td>NA</td>
<td>46 (78%)</td>
<td>NA</td>
<td>0.42</td>
</tr>
<tr>
<td>Postural Instability</td>
<td>29 (7%)</td>
<td>NA</td>
<td>7 (12%)</td>
<td>NA</td>
<td>0.19</td>
</tr>
<tr>
<td>Other</td>
<td>72 (17%)</td>
<td>NA</td>
<td>8 (14%)</td>
<td>NA</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Baseline Non-motor Characteristics

<table>
<thead>
<tr>
<th>Baseline Assessment</th>
<th>PD Subjects (N = 423)</th>
<th>Healthy Controls (N = 196)</th>
<th>SWEDD Subjects (N = 64)</th>
<th>PD p-value relative to HC</th>
<th>PD p-value relative to SWEDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOCA Total Score</td>
<td>27.1</td>
<td>28.2</td>
<td>27.1</td>
<td>&lt;0.01</td>
<td>0.94</td>
</tr>
<tr>
<td>SCOPA AUT Total Score</td>
<td>9.5</td>
<td>5.9</td>
<td>113.8</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GDS</td>
<td>2.3</td>
<td>1.3</td>
<td>3.3</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>State Trait Anxiety Score</td>
<td>65.2</td>
<td>57</td>
<td>70.3</td>
<td>&lt;0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>QUIP</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
<td>0.92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Benton Judgment of Line Orientation Score</td>
<td>12.7</td>
<td>13.1</td>
<td>12.8</td>
<td>0.05</td>
<td>0.84</td>
</tr>
<tr>
<td>HVLT Immediate Recall</td>
<td>9.7</td>
<td>10.2</td>
<td>9.7</td>
<td>&lt;0.01</td>
<td>0.84</td>
</tr>
<tr>
<td>HVLT Delayed Recognition</td>
<td>11.2</td>
<td>11.5</td>
<td>10.8</td>
<td>&lt;0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>HVLT Delayed False Alarms</td>
<td>1.2</td>
<td>1.1</td>
<td>1.7</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Letter Number Sequencing Raw Score</td>
<td>10.5</td>
<td>11</td>
<td>9.8</td>
<td>0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>Semantic Fluency Total Score</td>
<td>48.6</td>
<td>51.9</td>
<td>45</td>
<td>&lt;0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Symbol Digit Modalities (SDM)</td>
<td>41.3</td>
<td>46.8</td>
<td>41</td>
<td>&lt;0.01</td>
<td>0.83</td>
</tr>
<tr>
<td>UPSIT Raw Score</td>
<td>22.3</td>
<td>34</td>
<td>31.3</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale (ESS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Sleepy (9 or below)</td>
<td>345 (84%)</td>
<td>163 (88%)</td>
<td>40 (68%)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sleepy (10 or above)</td>
<td>65 (16%)</td>
<td>23 (12%)</td>
<td>19 (32%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REM Sleep Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (&lt; 5)</td>
<td>257 (62%)</td>
<td>152 (80%)</td>
<td>34 (58%)</td>
<td>&lt;0.01</td>
<td>0.57</td>
</tr>
<tr>
<td>Positive (5 or greater)</td>
<td>157 (38%)</td>
<td>37 (20%)</td>
<td>25 (42%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tables Generated on Data Submitted to PPMI as of: 01MAR2013.
MoCA Cut-off Scores

<table>
<thead>
<tr>
<th>MoCA</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>1</td>
<td>0.26</td>
<td>1</td>
<td>0.26</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>0.26</td>
<td>2</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>20</strong></td>
<td><strong>2</strong></td>
<td><strong>0.52</strong></td>
<td><strong>4</strong></td>
<td><strong>1.04</strong></td>
</tr>
<tr>
<td>21</td>
<td>5</td>
<td>1.30</td>
<td>9</td>
<td>2.34</td>
</tr>
<tr>
<td>22</td>
<td>8</td>
<td>2.08</td>
<td>17</td>
<td>4.43</td>
</tr>
<tr>
<td>23</td>
<td>13</td>
<td>3.39</td>
<td>30</td>
<td>7.81</td>
</tr>
<tr>
<td>24</td>
<td>13</td>
<td>3.39</td>
<td>43</td>
<td>11.20</td>
</tr>
<tr>
<td><strong>25</strong></td>
<td><strong>36</strong></td>
<td><strong>9.38</strong></td>
<td><strong>79</strong></td>
<td><strong>20.57</strong></td>
</tr>
<tr>
<td>26</td>
<td>49</td>
<td>12.76</td>
<td>128</td>
<td>33.33</td>
</tr>
<tr>
<td>27</td>
<td>64</td>
<td>16.67</td>
<td>192</td>
<td>50.00</td>
</tr>
<tr>
<td>28</td>
<td>68</td>
<td>17.71</td>
<td>260</td>
<td>67.71</td>
</tr>
<tr>
<td>29</td>
<td>70</td>
<td>18.23</td>
<td>330</td>
<td>85.94</td>
</tr>
<tr>
<td>30</td>
<td>54</td>
<td>14.06</td>
<td>384</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Consistent with research reporting 15-20% of de novo PD patients have MCI.
Longitudinal DAT

N = 117
Mean 13.3% ± 16.0%
78.6% going down at yr 1
CSF Acquisition

<table>
<thead>
<tr>
<th>Group</th>
<th>Visit (months)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  Baseline</td>
<td>6</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>PD</td>
<td>401 (98%)</td>
<td>275 (91%)</td>
<td>171 (87%)</td>
<td>29 (83%)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>184 (97%)</td>
<td>146 (87%)</td>
<td>140 (84%)</td>
<td>25 (80%)</td>
</tr>
<tr>
<td>SWEDD</td>
<td>59 (92%)</td>
<td>36 (89%)</td>
<td>25 (84%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

LP well tolerated – HA – 4-7%
CSF Volume collected 15.25 (mean)
Sprotte needle used in 82%
Syringe suction 63%
Sitting position in 63%
Flouroscopy in 5%
## CSF Pilot Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>HC (N = 39)</th>
<th>PD (N = 63)</th>
<th>$P$ value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{A}\beta_{1-42}$ (pg/mL)</td>
<td>$242.8 \pm 49.95$ (226.7 – 259.0)</td>
<td>$228.7 \pm 45.63$ (217.2 – 240.2)</td>
<td>0.0466</td>
</tr>
<tr>
<td>$t$-tau (pg/mL)</td>
<td>$53.9 \pm 19.33$ (47.6 – 60.1)</td>
<td>$46.1 \pm 24.71$ (39.8 – 52.3)</td>
<td>0.0276</td>
</tr>
<tr>
<td>$p$-tau$_{181}$ (pg/mL)</td>
<td>$24.9 \pm 8.45$ (22.2 – 27.6)</td>
<td>$21.0 \pm 7.83$ (19.0 – 23.0)</td>
<td>0.0093</td>
</tr>
<tr>
<td>$t$-tau/$\text{A}\beta_{1-42}$ ratio</td>
<td>$0.240 \pm 0.141$ (0.195 – 0.286)</td>
<td>$0.215 \pm 0.157$ (0.176 – 0.255)</td>
<td>0.0451</td>
</tr>
<tr>
<td>$p$-tau$<em>{181}$/A$\beta</em>{1-42}$ ratio</td>
<td>$0.113 \pm 0.075$ (0.089 – 0.138)</td>
<td>$0.099 \pm 0.063$ (0.084 – 0.115)</td>
<td>0.1482</td>
</tr>
<tr>
<td>$p$-tau$_{181}$/t-tau ratio</td>
<td>$0.491 \pm 0.160$ (0.439 – 0.543)</td>
<td>$0.543 \pm 0.263$ (0.477 – 0.609)</td>
<td>0.6820</td>
</tr>
<tr>
<td>$\alpha$-syn (pg/mL)</td>
<td>$1264 \pm 425.7$ (1126 – 1403)</td>
<td>$1082 \pm 611.1$ (928 – 1235)</td>
<td>0.0120</td>
</tr>
</tbody>
</table>
Natural history of Parkinson’s disease
Natural History of Parkinson disease

Neuron Function

Prodromal

Symptomatic

Diagnosis

P-PPMI

PPMI

Clinical Ratings

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research
Eligibility for P-PPMI

Hyposmic Subjects

RBD Subjects

DAT imaging

80% Mild to moderate DAT
20% Min to No-DAT

Eligible for PPMI

Min to No-DAT

Not eligible for PPMI
PPMI - Cohorts
Stage of PD
PPMI-LRRK2/SNCA

• Leverage existing PPMI infrastructure and add sites with existing expertise and experience with LRRK2 patients and families.

• Enroll 250-300 LRRK2/SNCA + PD and 250-300 LRKK2/SNCA + unaffected family members with and intensive longitudinal clinical assessment protocol.

• Follow PD and unaffected family members for for 3-5 years
  – Establish pre-motor biomarker signature
  – Define phenoconversion

• Maintain PPMI database structure and commitment to rapid access to data
**Current Status**

- PD, healthy and SWEDD cohorts and has established standardized procedures for acquisition and analysis of all study data

- PPMI strategy for comprehensive biomarker acquisition including CSF has been successful.

- PPMI longitudinal follow-up underway-subject retention - 16/662 subjects withdrawn from the study

- Robust web-based access(www.ppmi-info.org) for data and biospecimen - >70000 data downloads >20 biologic specimen requested.

- PPMI Prodromal and Genetic cohorts incorporated to assess prodromal PD biomarkers
PPMI ↔ ADNI

- Data Mining
- Imaging core – Amyloid imaging, DAT imaging, Tau, Inflammatory
- CSF – Tau, pTau, Amyloid, alpha-synuclein
- Cognitive outcomes
- Genetics – full sequence data
- Prodromal cohorts – ethical issues