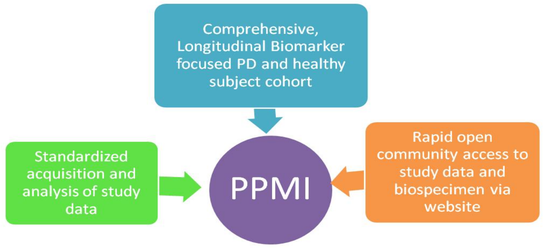
The Parkinson Progression Marker Initiative (PPMI)

BACKGROUND / RATIONALE

PPMI is an observational international multi-center study to identify clinical, imaging and biologic markers of Parkinson disease progression

Ultimate goal of PPMI is to develop PD progression markers that could be utilized to accelerate research on disease modifying PD therapeutics.

OBJECTIVES OF PPMI



Deliverable: Identify a biomarker tool set that can be used to inform decisions at early stages of drug development and clinical testing

STUDY DESIGN

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 imaging, DTI/RS MRI
Biologic Collection	▪ DNA collected at screening ▪ Serum, whole blood & plasma collected at each visit; urine annually ▪ CSF collected at baseline, 6mo, 12 mo and then annually
Initial Biospecimen Studies	▪ Lead biologic candidates to be tested: – Alpha-synuclein, Abeta 1-42, Total tau, Phospho-tau (p-181) (CSF) – DJ-1 (CSF and blood) – Urate (blood)
PD Treatment	▪ *De novo* for ~6 months ▪ Can participate in clinical trials (including interventional trials) after 12 months

PPMI Clinical Sites

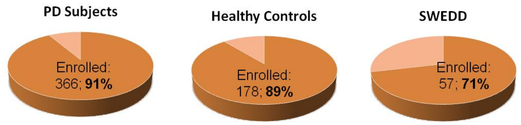
United States
University of Rochester – Rochester NY
Oregon Health Sciences University – Portland OR
Baylor College of Medicine – Houston TX
The Parkinson's Institute – Sunnyvale CA
University of Pennsylvania – Philadelphia PA
University of South Florida – Tampa FL
University of California San Diego - San Diego CA
Johns Hopkins University – Baltimore MD
Emory University, School of Medicine – Atlanta GA
Institute for Neurodegenerative Disorders - New Haven CT
Boston University – Boston MA
University of Alabama at Birmingham – Birmingham AL
Northwestern University – Chicago IL
Univ. of Wash & VA Puget Sound Health Care System – Seattle WA
Cleveland Clinic – Cleveland OH
University of Cincinnati – Cincinnati OH
Banner Research Institute- Phoenix AZ
Parkinson's Disease & Mov. Dis. Center of Boca Raton- Boca Raton FL

Europe
Innsbruck Medical University – Innsbruck Austria
University of Napoli – Napoli Italy
University of Tubingen – Tubingen Germany
Paracelsus-Elena Klinik – Kassel Germany
Imperial College of London – London England

Australia
Macquarie University – Sydney NSW Australia

RESULTS

Baseline Subject Recruitment



PD subjects 366 of 400; Healthy controls 178 of 200; SWEDD 57 of 80
as of 01MAR2013

PPMI data downloaded from PPMI website at:

http://www.ppmi-info.org/

Characteristics by Group at the Baseline Visit

Baseline Assessment	PD Subjects (N = 366)	Healthy Controls (N = 178)	SWEDD Subjects (N = 57)	p-value (PD relative to HC)	p-value (PD relative to SWEDD)
Mean Age (Range)	61.8 (33 - 85)	60.2 (31 - 84)	60.7 (38 - 79)	0.08	0.44
Gender (M %/F %)	241 (66%) / 125	113 (59%) / 63	35 (61%) / 22	0.63	0.55
MDS-UPDRS Mean Score & Sub Scores					
MDS-UPDRS Total Score	32.8	4.7	28	<0.01	0.01
MDS-UPDRS Part I	5.6	3	8.3	<0.01	<0.01
MDS-UPDRS Part II	6	0.4	5.7	<0.01	0.55
MDS-UPDRS Part III (Motor Exam)	21.2	1.3	14	<0.01	<0.01
Hoehn & Yahr N(%)					
Stage 0	0 (0%)	173 (97%)	0 (0%)	<0.01	0.1
Stage 1	155 (42%)	2 (1%)	32 (56%)		
Stage 2	204 (56%)	0 (0%)	23 (40%)		
Stage 3-5	2 (1%)	0 (0%)	0 (0%)		
Modified Schwab & England (mean)	93	NA	95	NA	0.09
Family Member with PD (%)	89(24%)	8 (4%)	16 (28%)	<0.01	0.59
Mean Duration of Disease (months)	6.8 (0.4 - 35.8)	NA	8.1 (0.5 - 37)	NA	0.18
Side most affected					
Left	149 (41%)	NA	10 (18%)	NA	<0.01
Right	205 (56%)	NA	42 (74%)		
Symmetric	9 (2%)	NA	5 (9%)		
Initial Symptoms*					
Resting Tremor	282 (77%)	NA	48 (84%)	NA	0.28
Rigidity	273 (75%)	NA	32 (56%)	NA	<0.01
Bradykinesia	294 (80%)	NA	45 (79%)	NA	0.69
Postural Instability	26 (7%)	NA	7 (12%)	NA	0.18
Other	61 (17%)	NA	8 (14%)	NA	0.59

* Subjects may have more than one initial symptom listed.

Non-motor Baseline Assessments at the Baseline Visit

Baseline Assessment	PD Subjects (N = 366)	Healthy Controls (N = 178)	SWEDD Subjects (N = 57)	p-value (PD relative to HC)	p-value (PD relative to SWEDD)
MOCA Total Score	27.1	28.3	27.1	<0.01	0.82
SCOPA AUT Total Score	9.6	5.9	13.8	<0.01	<0.01
GDS	2.2	1.3	3.3	<0.01	0.07
State Trait Anxiety Score	65	57.3	70.2	<0.01	0.05
QUIP	0.3	0.3	0.5	0.67	0.01
Benton Judgment of Line Orientation Score	12.7	13.1	12.9	0.03	0.48
HVLT Immediate Recall	9.7	10.2	9.7	<0.01	0.83
HVLT Delayed Recognition	11.2	11.5	10.9	<0.01	0.1
HVLT Delayed False Alarms	1.2	1.1	1.7	0.25	0.03
Letter Number Sequencing Raw Score	10.6	10.9	9.9	0.16	0.08
Semantic Fluency Total Score	48.5	51.7	44.9	<0.01	0.03
Symbol Digit Modalities (SDM)	41.2	47.2	40.9	<0.01	0.81
UPSIT Raw Score	22	33.9	31.1	<0.01	<0.01
Epworth Sleepiness Scale (ESS)					
Not Sleepy (9 or below)	298 (83%)	153 (87%)	37 (69%)	<0.01	<0.01
Sleepy (10 or above)	63 (17%)	22 (13%)	18 (33%)		
REM Sleep Disorder					
Negative (< 5)	223 (61%)	141 (79%)	35 (61%)	<0.01	1.00
Positive (5 or greater)	143 (39%)	37 (21%)	22 (39%)		

Tables Generated on Data Submitted to PPMI as of: 01MAR2013.

Mean unless otherwise stated

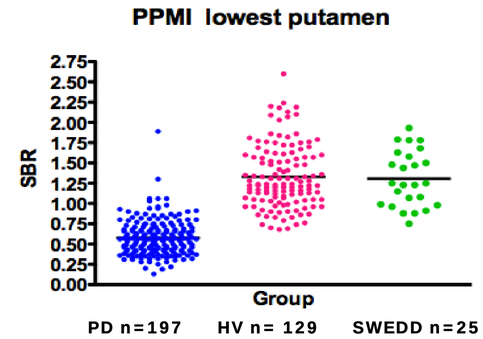
CSF Acquisition

Group	Baseline	Month 6	Month 12	Month 24
PD	357 (99%)	238 (92%)	143 (85%)	20 (85%)
Healthy	176 (97%)	145 (87%)	132 (83%)	16 (81%)
SWEDD	54 (91%)	31 (90%)	15 (93%)	N/A

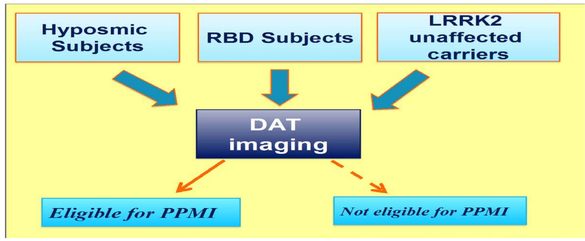
Pilot CSF

	HC (N = 39)	PD (N = 63)	*P* value[#]
$A\beta_{1-42}$ (pg/mL)	242.8 ± 49.95 (226.7 – 259.0)*	228.7 ± 45.63 (217.2 – 240.2)	**0.0466**
t-tau (pg/mL)	53.9 ± 19.33 (47.6 – 60.1)	46.1 ± 24.71 (39.8 – 52.3)	**0.0276**
p-tau_{181} (pg/mL)	24.9 ± 8.45 (22.2 – 27.6)	21.0 ± 7.83 (19.0 – 23.0)	**0.0093**
t-tau/$A\beta_{1-42}$ ratio	0.240 ± 0.141 (0.195 – 0.286)	0.215 ± 0.157 (0.176 – 0.255)	**0.0451**
p-tau_{181}/$A\beta_{1-42}$ ratio	0.113 ± 0.075 (0.089 – 0.138)	0.099 ± 0.063 (0.084 – 0.115)	0.1482
p-tau_{181}/t-tau ratio	0.491 ± 0.160 (0.439 – 0.543)	0.543 ± 0.263 (0.477 – 0.609)	0.6820
α-syn (pg/mL)	1264 ± 425.7 (1126 – 1403)	1082 ± 611.1 (928 – 1235)	**0.0120**

Baseline DAT imaging



Prodromal- PPMI cohort



PPMI-Genetic cohorts

LRRK2 - 400 -500 LRRK2 PD and LRRK2 unaffected carriers
Synuclein – 100 Synuclein PD and Synuclein unaffected carriers

CONCLUSION

- **PPMI, a comprehensive, international collaborative PD biomarker study has successfully enrolled >90% of planned subjects and has established procedures for acquisition and analysis of data that are fully operational.**
- **Requirement for baseline and longitudinal lumbar puncture has not been a major deterrent for recruitment of either PD or healthy subjects.**
- **It has been possible to establish a robust web-based process (www.ppmi-info.org) for data and biospecimen access while the study is ongoing and >50,165 data downloads worldwide and 21 biologic specimen have been requested.**
- **PPMI Prodromal and genetic cohort are planned in 2013**

PPMI Funding Partners

Full list of authors can be found at
http://www.ppmi-info.org/

PPMI is sponsored and partially funded by The Michael J. Fox Foundation for Parkinson's Research. Other funding partners include a consortium of industry partners

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
Abbott · biogen idec · GE Healthcare · Genentech · COVANCE · GlaxoSmithKline · MERCK · ucb · Lilly · Roche · elan · Pfizer · Avid Radiopharmaceuticals