Summary of the National Institute of Neurological Disorders and Stroke Parkinson's Disease Biomarkers Program Consortium Meeting August 8-9, 2016 Bethesda MD

On August 8-9, 2016, representatives from NIH, Principal Investigators (PIs), advocacy groups, industry, as well as clinical and data management experts from each project sponsored under the National Institute of Neurological Disorders and Stroke (NINDS) Parkinson's Disease (PD) Biomarkers Program (PDBP) met to discuss progress over the last twelve months in addition to current and future plans for the program. Since its establishment in 2012, the PDBP has sought to to promote the discovery of PD biomarker candidates for early detection and measurement of disease progression. Clinical and biosample data are housed in a common Data Management Resource (DMR) web-based database. The PDBP serves as a platform for: integrating existing biomarker efforts, standardizing data collection and management, accelerating the discovery of new biomarkers, as well as fostering and expanding collaborative opportunities for all stakeholders with the overarching goal of improving clinical trial design in PD and related disorders. A summary of the meeting discussion is given below.

Meeting Format

The format of this year's meeting was different in that steering committee members divided into four biomarker area panels: Imaging, Clinical, Genetic and Transcriptomic, and Proteomic and Metabolomics. Each panel was tasked with surveying their respective biomarker field, nominating the best PD biomarkers from their respective area, as well as determining future directions for biomarker research in this area. Industry representatives were also on-hand to provide feedback on the biomarkers presented by panel members and discuss their utility in designing effective clinical trials.

- **Imaging**
  - Biomarkers nominated: structural MRI, tasks and resting state fMRI, and PET imaging as diagnostic, heterogeneity, progression, and target engagement markers
  - Future directions include:
    - Multimodal imaging will be key across multiple sites for validation efforts
    - Combine imaging with other biomarker types
    - Reproducibility needed

- **Clinical**
  - Current and nominated biomarkers: measures of
    - Hyposmia (UPSIT)
    - RBD (RBD screening questionnaire; polysomnagram)
    - Motor symptoms (UKBB criteria, MDS-UPDRS)
    - Cognitive symptoms (MoCA)
  - Future directions may include utilization of more objective clinical measures including 'wearable' technology (i.e. mPower and other smartphone based assessments)

- **Genetic and Transcriptomics**
  - Nominated markers:
    - Genetic variants of *GBA*, *MAPT, and SNCA* as PD to monitor disease progression
    - Glucocerebrosidease (GCase) and sphingolipids in CSF and plasma as progression markers
    - *SNCA* transcript expression as a marker for cognitive decline
  - Future directions recommended:
    - Increase sample size including large longitudinal *GBA* cohorts
    - Assay –omics markers (RNA-seq, WGS, Nanostring microRNA array) across large numbers of PD cohorts
    - Use genetics for patient stratification in clinical trials based on underlying genetic etiologies and genetics-driven personalized phenotypes
    - Identify genes useful as drug targets to slow disease progression

- **Proteomic and Metabolomics**
  - Nominated candidates tested in large cohorts and replicated in an independent cohorts
    - CSF phosphorylated-tau (p-tau), total-tau (t-tau) and p-tau/ABeta42 as progression markers of motor decline
    - Plasma Epidermal Growth Factor (EGF) as a baseline predictor of cognitive decline
    - Serum urate as predictor of motor decline
    - Serum or plasma Vitamin D as risk marker for PD
    - Plasma ApoA1 as a marker of motor impairment
  - Future directions recommended:
    - Replicate candidates nominates as markers of heterogeneity
    - Consider risk biomarkers as therapeutic targets
    - Markers where baseline levels predict disease severity, use this information to enrich clinical trials
    - Assess progression markers in longitudinal cohorts
    - More biomarkers of target engagement and differential drug response needed to improve clinical trials
    - More focus needed towards identifying biomarkers to aid in pre-symptomatic diagnosis of PD as well as progression of disease course

Overview of Performance - Year 4

Progress Across All Sites

- Nineteen peer-reviewed articles have been accepted in Year 4
- Four new projects associated with PDBP
    - Blood RNA biomarkers of Parkinson's disease (PD) and Progressive Supranuclear Palsy (PSP) (P.I. Dr. Judith Potashkin)
        - Goals are to identify diagnostic PD and PSP RNA biosignatures in whole blood
    - Parkinson's Disease: Predicting the Future (P.I. Dr. Clemens Scherzer)
        - Goals are to delineate genetic variants associated with progression in PD using targeted DNA sequencing
        - Validate these progression genetic variants in independent PD cohorts
    - Detection of Post-Translationally Modified Proteins as a Biomarker Panel for Parkinson's Disease (P.I. Dr. David Walt)
        - Discovery study to develop a PD biomarker panel of serum proteins using digital immunoassay technology (SiMoA)
    - Exosome LRRK2 in Predicting Parkinson Disease Phenotypes (P.I. Dr. Andrew West)
        - Replication study using urine and CSF exosomes
            - Determine if pS1292-LRRK2 levels can serve as a marker for PD risk over time in LRRK2 mutation carriers
            - Evaluate if PS1292-LRRK2 levels predict cognitive impairment in drug naïve idiopathic PD patients, as well as later stage PD patients

Site Recruitment and Biospecimen Collection

- As of August 8, 2016- 1,509 participants enrolled in the PDBP
- PDBP biospecimens are now housed at the NINDS Repository: Biospecimen Exchange for Neurological Disorders (BioSEND) at Indiana University
- Samples banked from over 1,400 PDBP subjects as of August 2016.
    - 1,444 DNA
    - 3,862 RNA
    - 3,263 Plasma
    - 2,942 Serum
    - 791 CSF
    - 3,258 whole blood

Data Management Resource

- As of August 7, 2016: 4,737,487 records and 402,050 datasets accessed through the DMR Query Tool: An increase of 184% from 2015!
- 110 DMR accounts have been approved
    - 29% - GUID Generation
    - 22% - Biosamples for biomarker research
    - 17% - PDBP collaborators
    - 17% - Exploratory
    - 12% - Data analysis tools
    - 3% - Data/Sample submission
- PDBP Biospecimen Resource Access Committee (BRAC)

- The NINDS X01 mechanism PAR14-340 has been discontinued. Requests for biospecimens can now be submitted on the PDBP website through the online Application for Access to Parkinson's Disease Biomarker Samples. Similar to the X01 mechanism, there are rolling submission deadlines: 6x per year, coordinated by the PDBP BRAC.
- The PDBP BRAC handles biospecimen access for the following cohorts
  - PDBP
  - Michael J Fox Foundation (MJFF): DATATOP, BioFIND, LRRK2, and 24 hr sampling study
  - Harvard Biomarker Study
- As of August 2016, 26 applications have been approved, as well as 15 letters of support contingent upon funding availability

Patient Perspective

- Two PD patients, Kathy Wenger and David Queen along with their families, participated in a discussion panel moderated by Dr. Xuemei Huang
- Patients and their families provided insight into how Parkinson's disease has affected their lives.
- Dr. Huang asked the patients and caregivers what motivated them to participate in PDBP
  - Mrs. Wenger heard about the study from a friend who was participating at Penn State Hershey.
  - Mrs. Queen saw the study as an opportunity to learn more about the disease while helping other patients.
- When asked about the biggest barrier for participating, caregivers expressed initial hesitation regarding undergoing a lumbar puncture (LP). However after the first LP and "taking a leap of faith" in their physician, they no longer have any reluctance.
- Patients suggested additional educational and news outreach be available on the PDBP website to stay informed of research progress
- Patients and their families were encouraged by the depth and detail of the research presented at the annual meeting.

Looking Forward to Year 5- Suggestions from the meeting

PDBP:

- Expand PDBP to include Lewy Body Dementia (LBD) and Parkinsonism patients.
- Continue monthly steering committee meetings, highlighting progress from investigator's research projects
- Develop a white paper based on the recommendations coming out of this meeting

PDBP DMR:

- Develop cloud computing solution for Whole Genome Sequencing (WGS) and PDBP data analysis
- Set up Meta Study platform for all discovery projects
- Expand form structures and ProFoRMS to include PSP scale, ET scale and recommendations from the LBD working group

- Completion of form structures for DNA, RNA, and immunoassays.
- Collection of PBMCs

PDBP Biorepository:

- Ensure uniform collection and processing of biospecimens by working closely with clinical coordinators from all sites
- Sample requests will continue via BRAC applications submitted on the PDBP website.
- BioSEND will continue to work with investigators who are preparing grant applications to provide quotes for sample banking and processing
- Weekly teleconferences with NINDS Program Staff and DMR team

Summary

A number of efforts from PDBP investigators (http://pdbp.ninds.nih.gov/projects-we-support) are underway towards PD biomarker discovery and validation in the areas of imaging, clinical, genomic and transcriptomics, and proteomics and metabolomics. Concurrently, the DMR serves as a hub to house clinical data (which are publicly available for analysis), as well as biospecimens collected and processed in a standardized manner (sample requests considered by the BRAC). As the PDBP enters its fifth year, additional 'omics data will be available in the DMR, including whole genome sequencing and proteomic data. Moreover, while continuing discovery and validation research, the PDBP steering committee is also mindful of evaluation of candidate biomarkers' application in clinical trials, including population stratification, monitoring disease progression and assessing target engagement.