Cell Line Resources from Parkinson's Progression Marker's Initiative (PPMI) Participants

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PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

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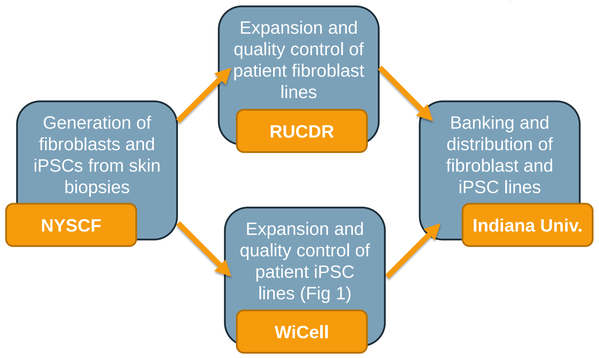
Introduction

The Parkinson's Progression Markers Initiative (PPMI) is a longitudinal observational study conducted at over thirty international sites that collects data and biospecimens from idiopathic Parkinson's patients, age- and gender-matched controls, and participants with risk factors for Parkinson's disease (PD), such as genetic mutations, hyposmia, and REM Sleep Behavior Disorder (RBD), for a minimum of five years. PPMI makes these data and biospecimens rapidly available to qualified investigators to enable biomarker research. In addition to blood products, nucleic acids, urine, and cerebrospinal fluid (CSF), PPMI is also committed to obtaining and distributing a range of cell lines, including uniformly collected fibroblasts and induced pluripotent stem cells (iPSCs), from these well-characterized participants to be used for biomarker research, therapeutic development, drug screening, and disease modeling. PPMI includes these collections as part of two separate Golub Capital iPSC sub-studies, described below.

Study 1: Development of Fibroblasts and iPSCs with NYSCF, RUCDR, & WiCell

The first study, beginning in 2014, is a PPMI collaboration with the New York Stem Cell Foundation (NYSCF), WiCell, Rutgers University Cell and DNA Repository (RUCDR), and Indiana University to generate, characterize, bank, and distribute fibroblasts and iPSCs from skin biopsies.



Skin biopsies were collected from 20 idiopathic PD patients and 5 controls from one U.S. site. NYSCF generated fibroblasts and iPSCs from the skin biopsy samples. Expansion, quality control, and characterization were performed by RUCDR and WiCell;. Lines were transferred to Indiana University for banking in the PPMI biorepository for distribution.

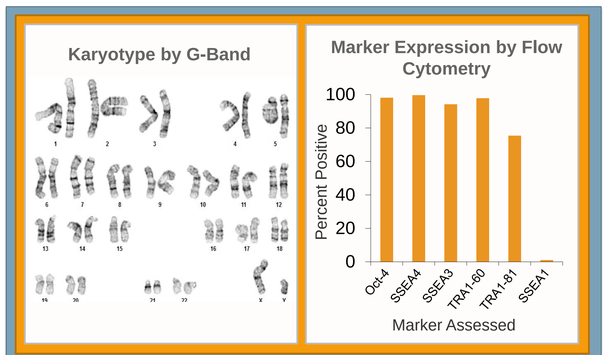


Fig 1. Example of the characterization performed by WiCell on the iPSC lines. Data presented is for the PPMI001i cell line and includes karyotype analysis by G-Band and assessment of markers of the undifferentiated status of the cell line by flow cytometry. Additional analyses include thaw recovery, STR (identity), sterility testing, and mycoplasma testing.

Study 2: Development of iPSCs with Cellular Dynamics International (CDI)

The second study was initiated in 2016 to expand the iPSC offerings through a collaboration with Cellular Dynamics International (CDI) and Indiana University. This second study used a blood-based collection protocol to obtain peripheral blood mononuclear cells (PBMCs) from 137 PPMI participants at ten international sites. Participants in this study include healthy volunteers, participants diagnosed with idiopathic PD, participants with clinical risk factors for PD (hyposmia and RBD), and participants with and without PD who have genetic risk factors for PD (GBA1, LRRK2, and SNCA mutations). Of note, each patient enrolled for PBMC collection and iPSC generation also has contributed corresponding clinical, imaging, and biosample data to PPMI.

PBMCs from patients enrolled in this sub-study were reprogrammed into iPSCs by CDI (n=3 clones per patient) and deposited at the Indiana University biorepository for access through PPMI. The breakdown of available iPSCs from each patient cohort is listed in Table 1. Lines were underwent quality control testing at CDI by karyotype analysis, identity confirmation (genotyping for 38 SNPs), pluripotency markers (gene expression of 48 mRNAs), and mycoplasma testing. All 137 lines are now available for request by qualified researchers through the PPMI biospecimen request process (more information in the Summary section).

Moving forward, MJFF is committed to continued investment for the PPMI iPSCs to generate isogenic control lines for the Genetic PD and Genetic Unaffected lines, as well as differentiating these iPSCs into various cell types, including dopamine neurons and glial cells.

Patient PBMC-Derived iPSCs	Isogenic Control iPSCs	Reprogrammed Neurons and Glia
♦ Control ♦ SWEDD ♦ iPD ♦ GBA PD ♦ LRRK2 PD ♦ SNCA PD ♦ GBA Unaffected ♦ LRRK2 Unaffected ♦ GBA+LRRK2 Unaffected ♦ SNCA Unaffected ♦ Hyposmia ♦ RBD	♦ GBA PD Corrected ♦ LRRK2 PD Corrected ♦ SNCA PD Corrected ♦ GBA Unaffected Corrected ♦ LRRK2 Unaffected Corrected ♦ GBA+LRRK2 Unaffected Corrected ♦ SNCA Unaffected Corrected	♦ Control ♦ SWEDD ♦ iPD ♦ GBA PD + Corrected ♦ LRRK2 PD + Corrected ♦ SNCA PD + Corrected ♦ GBA Unaffected + Corrected ♦ LRRK2 Unaffected + Corrected ♦ GBA+LRRK2 Unaffected + Corrected ♦ SNCA Unaffected + Corrected ♦ Hyposmia ♦ RBD
Available	**Est. Initiation 2019**	**Est. Initiation 2019/2020**

Patient Cohort	Mutation	# of Participants
Control	---	10
SWEDD	---	1
Idiopathic PD	---	41
Genetic PD		
GBA	N370S HET	15
	N370S HOM	1
LRRK2	G2019S HET	12
	R1441G HET	2
SNCA	G209A HET	3
Genetic Unaffected		
GBA	N370S HET	19
LRRK2	G2019S HET	22
GBA and LRRK2	N370S HET and G2019S HET	2
SNCA	G209A HET	2
Prodromal		
Hyposmia	---	5
RBD	---	2

Table 1. Cell lines available through the PPMI iPSC study. iPSC lines are available for subjects without PD age 30 years or older with no first degree relative with PD (Control), patients consented as PD patients with Scans Without Evidence of Dopaminergic Deficit (SWEDD), patients with idiopathic PD, patients with a genetic mutation diagnosed with PD (Genetic PD), patients harboring a genetic mutation without evidence of PD (Genetic Unaffected), and patients with risk factors for PD (Prodromal). Three iPSC clones are available for each patient.

Additional PPMI/MJFF Resources

Additional data and biologic samples are available within the PPMI cohort for biomarker validation/verification. A description of the PPMI study population, clinical data, biologic sample availability, and additional data are in Table 2.

Study Population	Clinical Data	Biologic Samples	Additional Data
♦ 400 de novo PD (newly diagnosed and unmedicated) ♦ 200 age-and gender-matched healthy controls ♦ 65 SWEDD ♦ 65 non-genetic with risk factors (hyposmia, RBD) ♦ 600 LRRK2, GBA, or SNCA (PD manifesting and non-manifesting family members) ♦ Subjects followed for 3-13 years	♦ Motor assessments ♦ Non-motor assessments: autonomic, cognitive, sleep neurobehavioral, neuropsychological, olfaction ♦ Imaging: AV-133 DaTSCAN, fMRI, SPECT, DTI	♦ Urine[a] ♦ Plasma[b] ♦ Serum[b] ♦ Whole Blood[b] ♦ PBMCs[a] ♦ CSF[c] ♦ DNA (from blood)[d] ♦ DNA (buffy coat)[a] ♦ RNA (from blood)[b] ♦ Fibroblasts[e] ♦ iPSCs[e]	♦ Alpha-synuclein (CSF) ♦ Uric Acid (blood) ♦ Abeta 1-42 (CSF) ♦ Total tau and phospho-tau (p-181) (CSF) ♦ SNP genotyping ♦ Whole exome sequencing ♦ Whole genome sequencing ♦ RNAseq

Table 2. Overview of PPMI Study, including information on study populations, clinical data collection, biologic sample collection, and additional analyses.
[a] Samples collected annually
[b] Samples collected at each visit
[c] Samples collected at baseline, 6 months, 12 months, and annually thereafter
[d] Samples collected during initial screening
[e] Available from a subset of patients (listed in center column)

Additionally, MJFF has data and biospecimen samples available by request for other patient populations and studies. These include:

- BioFIND for biomarker discovery
- DATATOP for biomarker discovery/validation
- LRRK2 Cohort Consortium for LRRK2-related biomarker discovery/validation
- 24-Hour Biofluid Sampling for diurnal fluctuations
- Arizona PD Consortium for clinicopathology correlations

Summary and More Information

For more information please visit:

- www.ppmi-info.org for information on the PPMI study as well as availability of PPMI data and biospecimens.
- www.michaeljfox.org/biospecimens for information on biospecimen availability for PPMI and additional cohorts.
- www.michaeljfox.org/data for information on data availability for PPMI and additional cohorts.