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

T. LUDWIG[1], A. REIMER[2], T. FOROUD[3], D. SMITH[3], C. WEGEL[3], C. MITCHELL[3], R. CASE[3], M. FRASIER[2], A. NAITO[2], S. LASCH[4], K. MAREK[4], C. DUNIFON[3]

[1]WiCell, Madison, WI; [2]Michael J. Fox Foundation, New York, NY; [3]Indiana Univ., Indianapolis, IN; [4]Inst. for Neurodegenerative Disorders, New Haven, CT

ABSTRACT

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-matched controls, and participants with risk factors for Parkinson's disease (PD), such as genetic mutations, hyposmia, and REM Sleep Behavior Disorder (RBD), for up to 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 fibroblast and iPSC collections as part of two separate ancillary studies. The first sub-study, performed in collaboration with the New York Stem Cell Foundation (NYSCF), derived fibroblasts and iPSCs from skin biopsies. Fibroblasts and iPSCs from twenty idiopathic PD patients and five controls from one U.S. site are currently available for request from this ancillary study. In order to provide cell lines to as many qualified researchers as possible, PPMI is prioritizing the expansion and characterization of these iPSC and fibroblast resources by WiCell and the Rutgers University Cell and DNA Repository (RUCDR), respectively.

The second ancillary study is currently being conducted in collaboration with Cellular Dynamics International (CDI). This expanded ancillary study uses a blood-based collection protocol and is being carried out at eight U.S. sites. The sites participating in this ancillary study aim to have 135 collections from idiopathic PD patients, controls, prodromal participants, and affected and unaffected carriers of genetic mutations associated with PD by the end of 2017. The iPSCs generated in collaboration with CDI are made available on a rolling basis as they complete reprogramming. All PPMI cell lines are housed at the biorepository at Indiana University.

LANDMARK STUDY OF PARKINSON'S DISEASE

The Michael J. Fox Foundation for Parkinson's Research (MJFF) is dedicated to finding a cure for Parkinson's disease (PD) through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson's today. Sponsored by MJFF and funded by MJFF and funding partners (see www.ppmi-info.org/fundingpartners), the Parkinson's Progression Markers Initiative (PPMI) is a landmark observational clinical study. Its purpose is to comprehensively evaluate cohorts of significant interest for PD research using advanced imaging, biologic sampling, and clinical and behavioral assessments to identify biomarkers of Parkinson's disease progression. With clinical sites in the United States, Europe, Israel, and Australia, data and samples acquired from study participants are enabling the development of a comprehensive Parkinson's database and biorepository. These tools are now available to the scientific community to conduct field-changing research.

GOLUB CAPITAL

PPMI cell lines are available through the Golub Capital iPSC PPMI Sub-study.

VALUABLE TOOLS FOR PARKINSON'S DISEASE RESEARCH

In 2014, PPMI, in collaboration with the New York Stem Cell Foundation (NYSCF), began generating fibroblasts and induced pluripotent stem cells (iPSCs) from skin biopsies from 20 PD and 5 control patients at one U.S. site. This pilot study closed in 2015.

In 2016, PPMI, in collaboration with Cellular Dynamics International (CDI), expanded to include the generation of iPSC lines from reprogrammed peripheral mononuclear blood cells (PBMCs) collected from PPMI participants. Study leadership hopes to complete 135 blood collections by the end of 2017; to date, over 90 PPMI participants have given blood samples. Cells lines from this expanded sub-study are derived from participants who have idiopathic PD, healthy volunteers, participants with clinical risk factors for PD, and participants with and without PD who have genetic risk factors for PD (GBA1, LRRK2, and SNCA mutations). This diversity of sources, and the corresponding clinical, imaging, and biosample data, make these iPSC lines an unparalleled resource for the study of PD. MJFF hopes that iPSC lines and PPMI clinical data can be leveraged together for biomarker research, drug screening, and disease modeling. Using iPSCs from the PPMI collection (Table 1), researchers can model PD in a dish, and use this tool to aid in the development and testing of new treatments. Streamlined access to these tools and materials will speed progress toward treatment and ultimately cure of this progressive disease.

Following derivation of iPSCs by NYSCF or CDI, MJFF partnered with WiCell to produce distributable cryobanks of the iPSC lines for use by the scientific community through PPMI. WiCell received seed vials of iPSCs, thawed, expanded, cryopreserved, and characterized materials intended for distribution. All iPSC lines banked by WiCell were banked and characterized according to WiCell's high quality assurance standards. Characterization assays performed on each line post-banking include thaw recovery, STR (identity), sterility testing, mycoplasma screening, karyotype by G-Band analysis, and flow cytometry to assure the undifferentiated status of the cell line. Once banking and characterization were complete, materials were transferred to the PPMI centralized repository at Indiana University, which manages the storage and distribution of PPMI iPSCs.

Table 1. Cell lines available through the Parkinson's Progression Markers Initiative at Indiana University

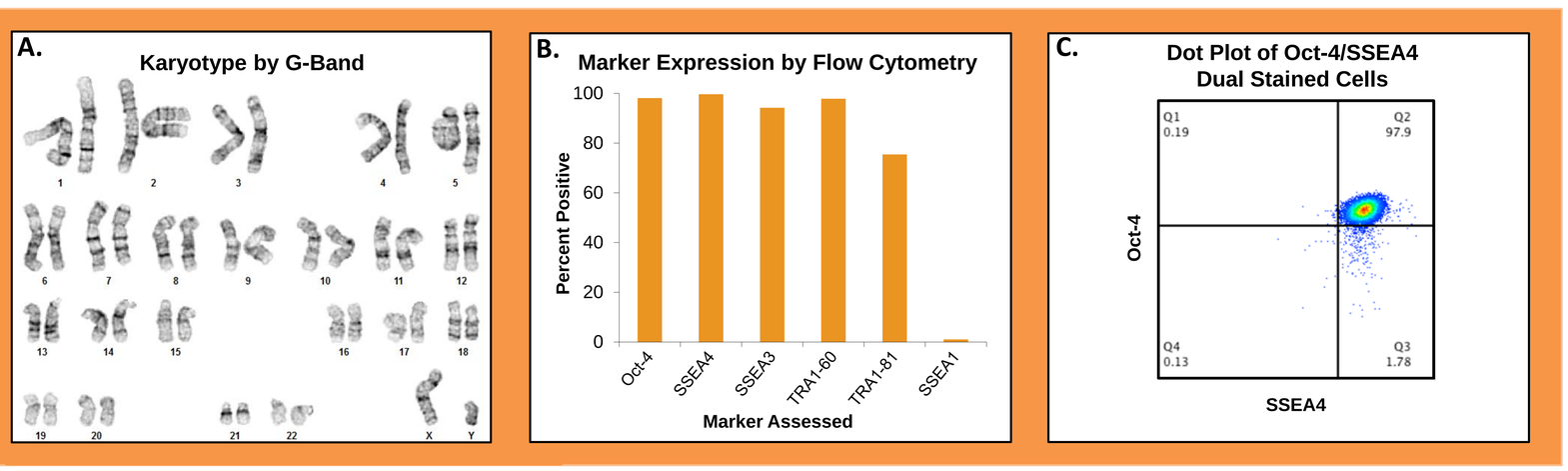
Biospecimen Data of Available Cell Lines			
Collection	Number of Subjects	Average Age at Onset	Average Age at Collection
Fibroblast	**25**	**59**	**63**
iPD[a]	20	59	63.7
Control[b]	5	-	60.2
iPSC	**119**	**59.5**	**65.1**
iPD[a]	53	59.8	65.6
Control[b]	15	-	65.9
SWEDD[d]	1	62	68
Prodromal	4	-	73.3
LRRK2[c] PD	12	60.7	65.3
LRRK2[c] Unaffected	16	-	64.6
LRRK2/GBA[c] Unaffected	1	-	64
GBA[c] PD	6	54.2	57.5
GBA[c] Unaffected	10	-	64.8
SNCA[c] Unaffected	1	-	44
Grand Total	**144**	**59.4**	**64.7**

a: Subjects with Idopathic Parkison's Disease
b: Control subjects without PD age 30 years or older with no 1st degree blood relative with PD
c: Subjects with genetic mutation in LRRK2, GBA, or SNCA
d: Subjects consented as PD subjects with Scans Without Evidence of a Dopaminergic Deficit (SWEDD)

GAINING ACCESS TO MATERIALS

All PPMI cell lines are currently available for request by the scientific community for use in research. To apply for access to PPMI cell lines, please visit http://www.ppmi-info.org/access-data-specimens/request-cell-lines/. Once an application has been completed and submitted, it will be reviewed by the PPMI Biospecimen Review Committee. Once the application is approved and appropriate material transfer agreements (MTAs) are in place, materials are shipped directly to the requesting researcher from the centralized PPMI repository at Indiana University.

Figure 1. Example characterization of WiCell banked PPMI cell lines.



Example of the characterization data performed by WiCell on the PPMI iPSC collection. Data presented is for the PPMI001i cell line. A.) Karyotype by G-Band performed by WiCell's Cytogenetics Laboratory. B.) Markers of the undifferentiated status of the cell line assessed by flow cytometry. C.) A dot plot representing the percentage of cells that stained positive for both Oct-4 and SSEA4 (each cell is dual stained). Either the 5 marker flow cytometry assay or Oct-4/SSEA4 dual staining assay was performed for all lines. WiCell also performed identity testing (STR), mycoplasma screening, and sterility testing on all MJFF/PPMI materials.