

Apr 22, 2024

Autoimmunity and The Role of T Cells in Parkinson's Disease (PPMI Whole Blood T cells)

DOI

dx.doi.org/10.17504/protocols.io.261ge543jg47/v1

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DOI: **dx.doi.org/10.17504/protocols.io.261ge543jg47/v1**

Protocol Citation: David Sulzer, Cecilia Arlehamn 2024. Autoimmunity and The Role of T Cells in Parkinson's Disease (PPMI Whole Blood T cells). protocols.io **<https://dx.doi.org/10.17504/protocols.io.261ge543jg47/v1>**

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Protocol status: Working

We use this protocol and it's working

Created: March 08, 2024

Last Modified: April 22, 2024

Protocol Integer ID: 98630

Keywords: ASAPCRN, autoimmunity, T cells, PPMI, Parkinson's Progression Markers Initiative, Parkinson's Disease

Funders Acknowledgement:

The Michael J. Fox

Foundation

Grant ID: na

Aligning Science Across

Parkinson's

Grant ID: na

4D Pharma

Grant ID: na

Abbvie

Grant ID: na

AcureX

Grant ID: na

Allergan

Grant ID: na

Amathus Therapeutics

Grant ID: na

AskBio

Grant ID: na

Avid Radiopharmaceuticals

Grant ID: na

BIAL

Grant ID: na

BioArctic

Grant ID: na

Biogen

Grant ID: na

Biohaven

Grant ID: na

BioLegend

Grant ID: na

BlueRock Therapeutics

Grant ID: na

Bristol-Myers Squibb

Grant ID: na

Calico Labs

Grant ID: na

Capsida Biotherapeutics

Grant ID: na

Celgene

Grant ID: na

Cerevel Therapeutics

Grant ID: na

Coave Therapeutics

Grant ID: na

DaCapo Brainscience

Grant ID: na

Denali

Grant ID: na

Edmond J. Safra Foundation

Grant ID: na

Eli Lilly

Grant ID: na



Gain Therapeutics

Grant ID: na

GE HealthCare

Grant ID: na

Genentech

Grant ID: na

GSK

Grant ID: na

Golub Capital

Grant ID: na

Handl Therapeutics

Grant ID: na

Insitro

Grant ID: na

Jazz Pharmaceuticals

Grant ID: na

Johnson & Johnson

Innovative Medicine

Grant ID: na

Lundbeck

Grant ID: na

Merck

Grant ID: na

Meso Scale Discovery

Grant ID: na

Mission Therapeutics

Grant ID: na

Neurocrine Biosciences

Grant ID: na

Neuron23

Grant ID: na

Neuropore

Grant ID: na

Pfizer

Grant ID: na

Piramal

Grant ID: na

Prevail Therapeutics

Grant ID: na

Roche

Grant ID: na

Sanofi

Grant ID: na

Servier

Grant ID: na

Sun Pharma Advanced

Research Company

Grant ID: na

Takeda

Grant ID: na

Teva

Grant ID: na

UCB

Grant ID: na

Vanqua Bio

Grant ID: na

Verily

Grant ID: na

Voyager Therapeutics

Grant ID: na

Weston Family Foundation

Grant ID: na

Yumanity Therapeutics

Grant ID: na

Abstract

This protocol details autoimmunity and the role of T cells in Parkinson's Disease (PPMI Whole Blood T cells).

Guidelines

Appendix 1-Schedule of Activities

PPMI Whole Blood T Cells Schedule of Activities

Visit	Sample 1 (VS1)	Sample 2 (VS2)*	Sample 3 (VS3)*
Assessment			
Consent Activities			
Documentation of Informed Consent	X		
Informed Consent Tracking Log	X		
General Activities			
Review Inclusion/Exclusion Criteria	I		
Screen Fail	As Needed		
Conclusion Page	As Needed		
Biological Samples			
Whole blood sample	X	X	X
General Health			
Vaccination history	X	X	X

I = Investigator completed assessment

X = Investigator or Coordinator completed assessment (or as otherwise delegated)

*participants may be asked to return for additional blood sampling

PURPOSE OF STUDY

- 1 The purpose of this protocol is to study T cell reactivity to α -synuclein in prodromal and early Parkinson's Disease (PD) participants compared to Healthy Controls (HC).
 - Autoimmunity plays a crucial role in PD through T cell responses toward α -syn^{1,2,8}.
- 2 Analysis of longitudinal changes in peripheral blood mononuclear cells (PBMCs) to identify autoimmune antigens, epitopes, and T cell receptors (TCRs) in Parkinson's Disease (PD) to investigate the association of Parkinson's Disease (PD) with general inflammation.

BACKGROUND AND AIMS

- 3 Research has played critical roles in advancing understanding of the role of the adaptive immune system in PD. It has been reported the presence of α -syn-responsive T cells in human PD, particularly for epitopes containing residue Y39 or phosphorylated S129 (pS129)^{1,2}, a component of Lewy bodies.
 - Y39 peptides are presented by specific HLA alleles associated with PD by GWAS studies³.
 - Findings of α -syn-responsive T cells in PD has been independently replicated⁴. It has been reported recently that α -syn-reactive T cells are mostly present during prodromal and early PD¹ during the rapid loss of SN DA neurons⁵.
 - While there are suggestions of additional PD-associated epitopes (e.g.,⁶), there has been one instance where these were assayed in human (see also⁷). An important question is whether PD patients exhibit a general change in T cell responses or if it is specific to disease-associated proteins.
 - To address this, we will examine if T cells from PD patients exhibit differential response to common antigenic proteins, e.g., pollens, CMV, EBV, pertussis, and influenza, which may be associated with PD and to which there is nearly universal response due in part to vaccination.

3.1 Aim 1:

To determine changes in epitope-specific T cell reactivity against proteins for which processing is altered in neurodegenerative diseases including PD such as α -syn(including fibrils, which activate T cells¹), tau, amyloid- β and amyloid precursor protein, optineurin, GBA, LRRK2, TDP-43, OGDH, dysbindin, and ataxins.

- Publications confirm autoimmune T cell responses in individuals with PD against α -syn, and tau^{1,2,7}, but other candidates exist, and no studies have been performed on longitudinal samples.
- PBMCs from PD patients with recently diagnosed (<5 years) and long-term PD (>10 years), at-risk patients with REM sleep behavior disorder (RBD), and age-matched HC in longitudinal

analysis will be examined. As not all PD patients respond to α -syn^{1,2}, other candidates contribute to autoimmune response will be explored by studying multiple antigens side-by-side, to determine if individuals possess poly-specific responses, or respond to a unique set of antigens.

- Enrolled participants will provide one blood draw but may be asked to provide additional blood draw at their annual PPMI visit(s). Magnitude and response quality by measuring proinflammatory (IFN γ , IL-5, and TNF α) and regulatory (IL-10) cytokines will be examined. Also, the antigen-specific TCR-repertoire will be examined to determine if TCRs promise a PD biomarker.
- Longitudinal samples will test if antigen-specific reactivity in recently diagnosed PD decreases over time, as predicted by a recent study², if reactivity predicts PD onset in RBD participants, and if the proinflammatory / regulatory cytokine ratio changes with a higher proportion of regulatory cytokines over time.
- We will determine if antigen-specific T cells are present during the prodromal phase in individuals at risk of developing PD and if detection of these cells may provide earlier diagnosis of PD.

3.2 **Aim 2:**

It is unknown if T cell changes in PD are specific to α -syn or represent altered general immune function. Inflammatory features are described in the brain of PD patients⁹ and anti-TNF treatment reduces PD incidence¹⁰, suggesting a preclinical heightened TNF response.

- Preliminary results suggests that PD patients who do not respond to α -syn (which may correspond to later stages) may display a depressed overall immune response. Characterization of antigen-specific responses will be determined in the same participants as above for Aim 1.
- Vaccination history, including seasonal influenza vaccination, will be recorded to investigate if induced vaccine responses differ between the cohorts. T cell reactivity will also be measured against α -syn, fibrils and epitopes and common antigens due to exposure (pollens, CMV, EBV), and vaccination (pertussis, tetanus, influenza) by Fluorospot and by intracellular cytokine assays for proinflammatory and regulatory cytokines including TNF α .
- Basal levels of T cell activation and reactivity by measuring T cell activation markers (OX40, PD-L1, CD137, CD25 and CD69) on unstimulated cells and response magnitude against polyclonal stimulation (PHA, anti-CD3/CD28 and PMA/IO) will be investigated.
- Participants will be analyzed based on reactivity to PD-specific antigens (α -syn and others in Aim 1) levels. Participants associated with neurodegeneration-antigen-specific T cell reactivity will be classified as exhibiting ongoing autoimmunity and compared to non-responsive PD patients (presumably past autoimmune responders and/or patients for whom T cell inflammation does not play a key role).
- This Aim will determine if PD is associated with general inflammation and altered immune response against frequently encountered foreign antigens.



STUDY DESIGN

- 4 This study will take place at up to 40 PPMI sites and will aim to enroll about 180 participants. It will involve 1 standard venous blood draw of approximately 50ml at the participant's baseline or annual visit (depending on when they enroll). Participants may be asked for an additional blood draw at future visits.

STUDY POPULATION

- 5 Approximately 180 participants enrolled in the PPMI Clinical will be recruited, including the following:
- 5.1 Prodromal participants n=approximately 120.
1. RBD (n= approximately 60).
 2. Hyposmic (n= approximately 60).
- 5.2 Parkinson's Disease Participants n= approximately 30.
- 5.3 Healthy Controls n= approximately 30

RECRUITMENT METHODS

- 6 A total of 180 participants will be recruited, all of whom are already enrolled in PPMI Clinical and may be at various stages of participation and follow up.
- PPMI Clinical participants who are potentially eligible will be provided information regarding this sub-study and invited to participate.
 - The clinical site staff will be responsible for recruiting participants into this sub-study.

PARTICIPANT ELIGIBILITY

- 7 Participants must meet the following criteria to enroll:
- 8 Inclusion Criteria:
- 8.1 Enrolled in PPMI Clinical.

8.2 Willing and able to provide informed consent.

9 Exclusion Criteria:

9.1 Known autoimmune condition, including rheumatoid arthritis, psoriasis, inflammatory bowel disease, systemic lupus erythematosus, etc.

9.2 Known immune deficiency disorder.

9.3 History of solid or hematological malignancy other than in situ carcinoma of the cervix or basal cell carcinoma of the skin (solid-within 1 year since removal).

9.4 Taking immunomodulatory medication, such as Humira (adalimumab), Enbrel (etanercept), Stelara (ustekinumab), Azathioprine, Cyclosporine, Cytoxan, Methotrexate, Tysabri (natalizumab), Rituxan (rituximab), beta-interferons, etc.

9.5 History of receiving chemotherapy agents with ability to affect the immune system, or radiation therapy (within 1 year after the last chemotherapy or radiation therapy).

9.6 Taking antibiotics or over the counter (OTC) "probiotic" preparations within 3 months of enrollment.

OBTAINING INFORMED CONSENT

10 The procedures and requirements of the study, together with any potential hazards/risks, and the freedom to withdraw from participation in the study at any time, will be explained to each potential participant as part of the consent process.

11 The consent process will take place in a space that allows for privacy and confidentiality and should allow for enough time for the individual to consider participation and ask any questions.

12 Consent will be obtained by the study Investigator or delegated study staff, as applicable. Each participant will sign such an informed consent to document agreement to participate in the study, as well as to document HIPAA authorization. The signed informed consent might be uploaded to a secure portal for remote monitoring.

13 It is the responsibility of the Investigator (or as delegated to the person obtaining consent) to make sure that the participant understands what she/he is agreeing to and that written informed



consent is obtained before the participant is involved in any protocol-defined procedures. Each participant will be provided a copy of the consent form.

PARTICIPANT ID ASSIGNMENT

- 14 All participants will use their assigned PPMI study ID. The PPMI Participant ID number will be used to identify a participant on all study related documentation.

STUDY PROCEDURES

- 15 Assessments for this study will be performed as described below and in the PPMI Whole Blood T-Cells Schedule of Activities.
- 16 Once consent is obtained, and eligibility is confirmed by the Site Investigator, the participant may be enrolled into the study.
- Participants will be asked to donate 50ml of blood via standard venous blood draw into five (5) 10ml EDTA tubes (purple top) at their visit of consent.
 - Each tube will be labeled with a de-identified participant ID and visit number. Post collection blood samples will be stored at ambient temperature (room temperature) at all times.
 - Samples will then be shipped via courier within 24 hours from the time of collection as per the PPMI Biologics Manual.

BIOLOGICS RESEARCH SAMPLING

- 17 **Refer to the PPMI Biologics Manual for a detailed description of blood sampling and shipping.**

17.1 Blood Samples

- Whole blood (about 50 ml) will be collected to conduct analyses as described above in Section 2. No more than 110 ml will be drawn at any visit, including this sub-study and the PPMI Clinical blood samples.
- All research samples will be sent to La Jolla Institute for Immunology (LJI) research lab to be stored indefinitely for research purposes. Samples will be made available to researchers to conduct analyses related to PD and other disorders. Participants will not receive any individual results of research analysis or testing conducted on the biologic samples.

CONCOMITANT MEDICATIONS

- 18 Concomitant medications refer to all medications take between the dates of signed consent and completion of study. All concomitant medications reported at the time of the PPMI Clinical Screening visit and for the duration of participation are recorded on the PPMI Clinical study medication logs.



- 19 Concomitant medications, including over the counter(OTC), dietary supplements (e.g., herbal remedies) or prescriptions, are permitted during the study period, except for the following medications: Taking immunomodulatory medication, such as Humira (adalimumab), Enbrel (etanercept), Stelara (ustekinumab), Azathioprine, Cyclosporine, Cytoxan, Methotrexate, Tysabri (natalizumab), Rituxan (rituximab), beta-interferons, etc. Taking antibiotics or OTC “probiotic” preparations within 3 months of study enrollment are prohibited.

RISKS TO PARTICIPANTS

- 20 Blood Sampling:

Risks associated with venous blood draw include pain and bruising at the site where the blood is taken. Sometimes people can feel lightheaded or even faint after having blood drawn.

- 21 Confidentiality:

There is a risk of loss of confidentiality. This risk will be minimized by removing individually identifying information from data and samples and replacing with a study code before sharing information with the LJI lab or a data repository.

POTENTIAL BENEFITS TO PARTICIPANTS

- 22 There are no direct anticipated benefits to study participants in this study. However, new information may be generated by the study that will support development of better treatments for Parkinson's Disease.

COSTS FOR PARTICIPATION

- 23 There are no additional costs for individuals participating in this study.

PAYMENT AND REIMBURSEMENT FOR PARTICIPATION

- 24 Participants will not be paid for activities completed in this study.

PARTICIPANT WITHDRAWALS

- 25 Study participants will be informed during the consent process that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's or Sponsor's discretion at any time. Any information that has already been collected prior to the study participant's withdrawal will not be removed.

PRIVACY AND CONFIDENTIALITY

- 26 Privacy of participants will be protected in that each person will have the option to voluntarily choose whether to participate in this study. It is the responsibility of the site Investigator to consider the participant's privacy and confidentiality when completing study visits and related protocol activities.
- 27 The Site Investigator must assure that the confidentiality of participants, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional confidentiality obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA).
- Participants will be identified by participant ID numbers on data forms and other study materials submitted to the La Jolla Institute for Immunology (LJI) research lab.
- 28 Only study staff requiring access to related study documentation will have permission to view identifiable information.

DATA AND SAMPLE SHARING AND STORAGE FOR FUTURE USE

- 29 Data collected for this study will be maintained and stored indefinitely at the study Cores on secure, password protected systems. All study information (data and samples) will be accessed only by those who require access as pertains to the individual's role on the study. All organizations responsible for data storage and review will observe the highest precautions to ensure data integrity and security.
- 30 Data collected for this study may be transferred and shared across participating PPMI Cores for conducting analyses as pertains to the study. All PPMI data will be incorporated into the PPMI database to create a fully harmonized PPMI database.
- 31 Data obtained during the conduct of this study will be sent to the Laboratory of Neuro Imaging (LONI) in Los Angeles, California to be stored indefinitely for research purposes.
- Research data will be made available to researchers to conduct analyses related to PD and other disorders. Researchers will be required to comply with the PPMI data agreement to receive data. All personally identifiable information will be removed before it is shared outside the study.

ANALYSIS PLAN

- 32 T cells will be assessed in RBD participants, as compared to PD and healthy control participants as described in Section 2 Aims. At the end of 3 years and following analysis, the RBD participants will be designated as a confirmed PD or non-PD diagnosis.

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