The Stanford Parkinson's Disease Plasma Study (SPDP)

NCT02968433

CLINICAL PROTOCOL

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Helen Bronte-Stewart, Principal Investigator
Stanford University

Stanford, California 94305

1. Protocol Title

The Stanford Parkinson's Disease Plasma (SPDP) Study: Intravenously-Administered Plasma From Young Donors for Treatment of Moderate Parkinson's Disease

Principal Investigator / Protocol Director: Helen Bronte-Stewart MD MSE
Sponsor: Donation (anonymous)

2. Purpose of the Study

The purpose of this study is to demonstrate that plasma infusions can be performed safely in patients with Parkinson's Disease (PD). Secondary outcomes will include behavioral and laboratory data that will support the next study that will inquire whether young plasma infusions improve or slow the progression of cognitive, mood and/or motor impairment and rate markers of the disease.

3. Background & Significance

Parkinson's disease (PD) is a neurodegenerative disease that affects over 1.6 million people in the United States and whose incidence increases with age, affecting over 1% of people over the age of 65. The neuropathological processes involved in PD are widespread throughout the brain, and are reflected in a constellation of motor, cognitive, mood and other non-motor symptoms. Treatments to date have largely focused on dopamine replacement strategies or deep brain stimulation, both symptomatic treatments.

As neurodegenerative diseases progress, there are major changes throughout the body and brain. These changes are transmitted in the body via the circulatory system between organs, tissues and cells. Recent findings from multiple laboratories have shown that infusions of young plasma into aging rodents can have beneficial effects on cognitive functions, as well as on some biomarkers of aging. This suggests that the circulating components of plasma can improve cognitive and disease-relevant symptoms (Villeda et al, 2011; Villeda et al, 2014). This has motivated the field to treat multiple disorders with blood products and their constituent active components.

The established safety of blood transfusions allows us to test whether infusion of young plasma can ease the neurological symptoms in human subjects with neurodegenerative diseases. A study that is ongoing at Stanford, in the department of Neurology and Neurological Sciences, is testing whether infusions of young plasma can ameliorate the cognitive impairment in patients with Alzheimer's disease (ClinicalTrials.gov identifier NCT02256306). To date, this has been well-tolerated by the subjects, without major adverse effects.

We propose to test the safety and efficacy of transfusing young plasma into PD patients, in order to establish its effects on motor and cognitive functions in patients in a Phase 1 study. The successful completion of this study will inform the design of future,

larger and multicenter studies with the goal to determine whether infusions of young plasma can ameliorate the neurodegenerative symptoms and underlying pathophysiology in Parkinson's disease.

4. Selection of Subjects

- The goal number of subjects completing the study is 15
- Subjects will sign an informed consent approved by the Stanford IRB

Inclusion criteria

- Subjects are to be between the ages of 50 – 80.
- A diagnosis of clinically probable or established Parkinson's Disease (MDS criteria)
- Subject must be on a stable dose of dopaminergic medication and/or DBS parameters for at least 4 weeks prior to screening and for the duration of the study
- Must have Montreal Cognitive Assessment (MOCA) score between 23-28, and have cognitive complaints
- Subject must be competent to sign consent
- Subject must be willing to commit to being available for twice weekly infusions and testing for 4 consecutive weeks and for testing one month later.
- The availability of a study partner who knows the patient well and is willing to accompany the subject to all trial visits, to participate in questionnaires and to complete daily journal assessments. *Note: optional partner participation if participant is able to consent and travel by self.*

Exclusion Criteria

- The participation in any other interventional therapeutic clinical trial during the study
- The inability to travel to Stanford
- Inability to walk without assistance in the off or on medication state
    - Must not exceed a Hoehn and Yahr score of 4
- The clinically determined presence of dementia
- A clinical suspicion/diagnosis of MSA, PSP LBD, ET
- Subject's pregnancy or likelihood of pregnancy within the next 6 months.
- Subject's positive test results for Hepatitis B, Hepatitis C or HIV at screening
- Any other condition or situation that the investigator believes may interfere with the safety of the subject or the intent and conduct of the study
- Subject's medical history of:
    - Stroke

  - Anaphylaxis
  - Gout- may cause an increase in uric acid
  - Prior adverse reaction to any human blood product
  - Any history of a blood coagulation disorder or hypercoagulability
  - Congestive heart failure
  - Uncontrolled hypertension
  - Renal failure
  - Prior intolerance to intravenous fluids
  - Recent history of uncontrolled atrial fibrillation
  - IgA deficiency (by history)
- Subject's relation to medications or other treatments:
  - Any concurrent use of an anticoagulant therapy. Antiplatelet drugs (e.g., aspirin or clopidogrel) are acceptable.
  - The use of Inosine, which may alter urate levels
  - Concurrent participation in another interventional treatment trial for Parkinson's disease. If there was prior participation, the last dose of the investigational agent must have been at least 6 months prior to Screening.
  - Treatment with any human blood product, including intravenous immunoglobulin, during the 6 months prior to Screening or during the trial.
  - Concurrent daily treatment with benzodiazepines, typical or atypical antipsychotics, long-acting opioids, or other medications that, in the investigator's opinion, interfere with cognition. Intermittent treatment with short-acting benzodiazepines or atypical antipsychotics may be permitted, provided that no dose is administered within the 72 hours preceding any cognitive assessment.

Ineligible Subjects

Ineligible subjects will be notified of their ineligibility. Ineligible subjects will be asked if their information could be kept on files in the event of being qualified to participate in future studies. If subjects do not want their information on file, all data collected will be destroyed. Only participating subjects will be used for analysis.

5. Design & Procedures

We will evaluate a dose of one Plasma unit transfusion twice per week (obtained from male subjects between the ages of 18-25) for four weeks in 15 study subjects with PD. The study will be open-label and an end point at eight weeks after the first week of transfusions.

The plasma will come from Stanford's Blood Center (SBC), not an external company. The Plasma product will be stored in the SBC, later transported to Stanford Transfusion Services before infusions. Infusions will take place in a Stanford Infusion Center. The primary objective of the study is to assess the safety and tolerability of twice weekly plasma transfusions. The secondary objectives are to assess the effect of twice weekly plasma transfusions in subjects with PD on motor function: United Parkinson's Disease Rating Scale (UPDRS), objective kinematic measures, cognitive function (detailed neuropsychological battery), and the Montreal

Cognitive Assessment (MoCA) as well as assessing plasma biomarkers through blood laboratory work.

- Donors must be:
  - Male- To minimize transfusion risks, only young male plasma will be used since female plasma has been linked to the possibility of Transfusion-Related Acute Lung Injury(TRALI), linked to immune cells carried by women who have been pregnant
  - Between the ages of 18-25
- Targeted availability of plasma within 2 weeks of completion of ABO/Rh typing.

Protocol

- **Initial screening** to evaluate the subject's candidacy based on the inclusion/exclusion criteria
- Health history and review of systems will be conducted
- Medication review
- Physical and neurological examinations: the Montreal Cognitive Assessment (MoCA), Unified Parkinson's Disease Rating Scale (UPDRS III and IV), and quantitative kinematics (physical): rapid Wrist Flex Extension (rWFE), Quantitative DigitoGraphy (QDG), Stepping in Place (SIP), and analysis of gait (GaitRite) ON and OFF medication (2 day visit), Freezing of Gait Questionnaire (FOG-Q), Stepping In Place questionnaire (SIP-Q)
  *Subject will be asked to bring their own dosage of short acting Parkinson's Disease medicine to take after kinematic testing (Carbidopa / Levodopa) for OFF MEDS visit.
  **When subject has signed consent and has been enrolled, notify the blood bank and transfusion service to order the plasma units.
- EKG

- **Baseline Assessment** (may occur immediately follow Screening, or occur on another day ***within 2 weeks*** of the first plasma transfusion) of the following will be conducted
  - Neurocognitive assessments: Trail Making Test A& B, Digit Symbol Test, Animal Naming Test, Phonemic Fluency (FAS), Matrix Reasoning, Block Design, Cogstate Maze Learning Test (Cog State)
  - Neuropsychiatric assessments: Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Parkinson's Disease Quality of Life Scale (PDQ-39)
  - Blood draw: 12 mL blood for central banking (these samples will be de-identified prior to further analysis and will be coded with a sample number, time of day and date of blood draw.
  - Blood Labs: metabolic and hematologic panels, Prothrombin Time (PT), Partial Prothrombin Time(PTT), Human Immunodeficiency Virus screen, Hepatitis B screen, Hepatitis C screen, IL6, uric acid, Apolipoprotein-

A1, direct bilirubin, homocysteine, ferritin, TNF, HIV Ag/Ab screen, ABO/Rh Typing and verification prior to first test agent administration

- **Plasma Transfusions** (***starting within 2 weeks*** of Baseline Assessment)
  - Administer test agent twice weekly for 4 weeks (see transfusion protocol below)
  - Concomitant medication review
  - Adverse event/tolerability review, Flow Sheet-recording of vitals
  - Adverse events review per transfusion center protocol

- **Interim Assessment (on the week of last transfusion)**
  - Motor/Physical (ON and OFF medication)- UPDRS III/ IV, SIP, rWFE, QDG, GaitRite/FW, SIP-Q, FOG-Q Neurocognitive assessments: Trail Making Test A& B, Digit Symbol Test, Animal Naming Test, Phonemic Fluency (FAS), Matrix Reasoning, Block Design, CogState Maze Learning Test (Cog State), ON medication
  - Neuropsychiatric assessments: Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), PDQ-39, ON medication
  - Blood Draw (Lab collect)
  - Blood draw: Metabolic and Hematologic Panels, inflammation set

- **Final Assessment (*4 weeks after* last tranfusion)**
  - Motor/Physical (ON and OFF medication)- UPDRS III/ IV, SIP, rWFE, QDG, GaitRite/FW, SIP-Q, FOG-Q
  - Neuropsychiatric assessments (BDI, BAI, PDQ-39), ON medication
  - Neurocognitive assessments Trail Making Test A& B, Digit Symbol Test, Animal Naming Test, Phonemic Fluency (FAS), Matrix Reasoning, Block Design, CogState Maze Learning Test (Cog State), ON medication
  - Blood Labs: Metabolic and Hematologic Panels, inflammation set,
  - Blood Draw:12 mL blood for central banking

- Transfusion Protocol
  - Perform the transfusion according to the most current “Blood and Blood Component Administration” guidelines at Stanford Hospital & Clinic; in brief:
    - Check and record pre-transfusion baseline vital signs (temperature and blood pressure) within 1 hour prior to transfusion.
    - Obtain IV access
    - Infuse test agent at 1-2 ml/min for the first 15 minutes while observing the subject closely for any adverse reaction.

- Record the vital signs at 15 min.
- If vital signs are normal or unchanged, then increase infusion rate to as fast as tolerated, or approximately 250-300 ml/hour.
- Continue to monitor the subject for signs/symptoms of adverse reaction during the entire infusion.
- For any suspected transfusion reaction, report immediately to the Principal Investigator, Dr. Helen Bronte-Stewart, or designated on-call study physician, Melanie Lising, and follow the detailed "Blood and Blood Component Administration" guidelines.
- Record vital signs 15 min after completion of the infusion
- The subject should remain at the infusion facility under nursing supervision throughout the entire transfusion procedure until 30 minutes after completion of the infusion. If post-transfusion vital signs are normal and there is no sign or symptom of an adverse reaction, then the subject t is free to go. Instructions will be provided to the subject and study partner about whom to contact and what to do in an emergency, if a delayed transfusion reaction is suspected.
- Retain a ~1 ml sample of the test agent in the unit after infusion.

6. Subject Recruitment and Compensation

Subjects will be recruited through Stanford's Clinic, The Michael J. Fox Foundation trial finder, listings in Clinicaltrial.gov, from previous experiments, and by personal interest in the study. Subjects recruited from previous experiments will have consented to be contacted for future experiments. Potential subjects will need to meet all inclusion criteria and none of the exclusion criteria. A reimbursement budget of $200 per subject will cover parking and travel related expenses.

7. Consent Process

Prior to introducing a consent form, the subject will receive a thorough description of the purpose of the study, the design of the study, potential risks and discomforts throughout and after the study, as well as the benefits (if any direct benefits) of participating of this study. After being informed, the subject will be presented with the consent form delineating previously stated information about the participation of this study. The subject undergoing the trial will be responsible for giving consent.

8. Subject's Capacity to Give Legally Effective Consent:

Upon the inability to provide consent, diminished capacity will be assessed by a series of cognitive assessments to provide a clear position on whether subject has enough cognitive capacity to participate in this study. Cognitive assessments will be administered prior to starting the study.

9. Study Interventions:

Implanted devices included but not limited to birth control methods, heart pacers, brain stimulators, etc. may intervene with the study. Subject will be asked if they have any implanted devices during prescreening.

10. Risk/Benefit Assessment:

Blood products carry risks of virus, hepatitis and HIV infection. Acute transfusion reactions could include such signs and symptoms as the following, divided into classes to denote the level of severity.

***Class 1:**

- Urticaria (a type of rash)
- Hives

Class 2:

- Fever
- Chills
- Nausea

Class 3:

- Low Hematocrit (which refers to the percentage of whole blood that is made up of red blood cells) without evidence of bleeding
- High bilirubin fever (meaning there is a higher level of waste that hasn't been filtered out as it usually is when red blood cells breakdown).

Class 4:

- Oliguria (a reduction in the amount of urine being passed)
- Bleeding
- Hemoglobinemia (an excess of hemoglobin in the blood plasma)
- Hemoglobinuria (hemoglobin—the oxygen-transporting protein in blood—is at abnormally high levels)
- Transfusion associated circulatory overload
- shock

***NOTE:** * Class 1 reactions are to be expected and considered within normal range for this study*

The subject will be observed during each transfusion for signs and symptoms of acute hemolytic reaction (i.e., chills, fever, low back pain, flushing, tachycardia, tachypnea, hypotension, red urine, shock, cardiac arrest). The subject will also be monitored

during the transfusion to minimize risk for potential infiltration or fluid overload due to rapid infusion of red blood cells (RBCs) or blood components.

Subjects with severe anemia and congestive heart failure are sensitive to circulatory overload.

The subject may also experience delayed transfusion reactions several hours to several days (delayed hemolytic reaction) after the transfusion is completed. Such reactions can include a febrile or pulmonary reaction (up to 6 hours) that may be associated with the blood administration.

Risks may include but not limited to transfusion reactions, bruising and/or soreness of arm in involved area, fatigue, boredom, and restlessness. To reduce the potential of any risks, subjects will be routinely asked for feedback on their current state. Some risks, such as arm bruising and soreness will be minimized by administration of procedure conducted only by qualified individuals. In the event of special precautions to be taken, such as the case of use of vulnerable populations (cognitively impaired adults), cognitive assessments before each session will be conducted to ensure the subjects ability to communicate any discomforts throughout the study.

- All adverse reactions reported after the start of the transfusions will be documented during trial.
- Transfusion reaction is an adverse event of a special interest, and any subject who experiences a transfusion reaction, in the opinion of the Transfusion Service or Dr. Bronte-Stewart and Dr. Lising, will not be allowed to receive any further infusion.
    - In the event of discontinuation of infusions due to a transfusion reaction or other serious adverse event, a safety and efficacy follow-up assessments will take place 1 week after the last transfusion.

11. Cost to the Subject:

There will be no cost for the subjects; the subject will not be expected to pay for research participation.

12. Data Analysis & Statistical Considerations:

Endpoints include

- Primary Outcome Measure:

- Number of subjects with adverse events as a measure of safety and tolerability, and number of subjects who comply with the research protocol as a measure of feasibility.

- Secondary Outcome Measures:

  - Change on the UPDRS III/ IV off medication
  - Change in gait speed
  - Change in quantitative kinematics, FOG-Q
  - Change on the Parkinson's Disease Quality of Life Scale (PDQ-39)
  - Change on the Beck Anxiety Inventory (BAI)
  - Change on the Beck Depression Inventory (BDI)
  - Change in Trail Making Test A& B, Digit Symbol Test, Animal Naming Test, Phonemic Fluency (FAS), Matrix Reasoning, Block Design and Cogstate Maze Learning Test (Cog State)
  - Change in plasma biomarkers

13. Data & Safety Monitoring

Safety concerns regarding subject data include loss of subject data and disclosure of identification of participants. All electronically connected data will be securely stored in Stanford Medicine Box with Protected Health Information (PHI) & Personally Identifiable Information (PII) protection. Persons with access to this information include the Primary Investigator, research coordinator, and research team collecting data. Frequency of data monitoring will be as needed for data processing.

To ensure the subject's data and physical safety, continuous safety monitoring will occur throughout the study by the Safety Review Committee. The Safety Review Committee will include an on-call Neurologists, Dr. Helen Bronte-Stewart, Dr. Melanie Lising, Psychologist Gayle Deutch, Sharon Sha and Neil Shah.

For any AEs outside of Stanford facility, the subject must call the research assistant at (650)723-6709. The research assistant will report AE to primary investigator and Dr. Lising. The subject will be told to seek medical assistance in nearest Emergency Department by them.

Research assistant will then need to file a SafeReport of the incident & document occurrence.

14. Privacy, Data Storage & Confidentiality

Subject confidentiality will be protected by electronically storing information using PHI and PII in Stanford Medicine Box. Persons with access to this information include the Primary Investigator, research coordinator, and research team collecting

data. Frequency of data monitoring will be as needed for data processing.

Table 1

	Screening		Baseline	Transfusions to start within 2 weeks after the baseline- 2 transfusions per week								Outcome visits Same week of last transfusion		Post Eval 1 month after last transfusion	
Visit	1 ON MEDS	2 OFF MEDS*	3	4 Week 1	5	6 Week 2	7	8 Week 3	9	10 Week 4	11	12 ON MEDS day after last transfusion	13 OFF MEDS* day after visit 12	14 ON MEDS Four weeks after Visit 12	15 OFF MEDS* Day after visit 13
Informed consent	X														
Medication review	X														
Health History	X														
Physical Exam	X														
Neurological exam	X														
UPDRS III	X	X										X	X	X	X
UPDRS IV	X											X		X	
EKG		X													
MOCA	X														
SIP	X	X										X	X	X	X
SIP-Q	X	X										X	X	X	X
FOG-Q		X											X		X
rWFE	X	X										X	X	X	X
QGD	X	X										X	X	X	X
GaitRite/ FW	X	X										X	X	X	X

Trails A and B			X									X		X	
Digit Symbol Test			X									X		X	
Animal Naming Test			X									X		X	
Phonemic Fluency (FAS)			X									X		X	
WASI-II Block Design			X									X		X	
CogState- Maze Learning			X									X		X	
Matrix Reasoning			X									X		X	
Beck Anxiety Inventory			X									X		X	
Beck Depression Inventory			X									X		X	
PDQ-39			X									X		X	
Blood draw (research collect)			X									X		X	
Blood Labs			X									X		X	
Concomitant Med Review			X	X		X		X		X					
Adverse Events/ Tolerability				X	X	X	X	X	X	X	X				
Flow Sheet				X	X	X	X	X	X	X	X				
Transfusion				X	X	X	X	X	X	X	X				