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TITLE: The Parkinson's Registry Investigation of Diagnosis and Etiology (PRIDE) Study

PRINCIPAL INVESTIGATOR: Caroline M. Tanner, MD, PhD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education  
San Francisco, CA 94121-1545

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# REPORT DOCUMENTATION PAGE

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<b>14. ABSTRACT</b> Exposure to pesticides, solvents or traumatic brain injury increase PD risk. This study takes advantage of the population-based PD registry in Santa Clara County, California and extensive state toxicants databases to investigate the causes of PD and PD-related morbidity and mortality. Study Design: Phase 1: The residence history of more than 3,000 PD cases from the population-based PD registry will be linked to geographically-specific exposure information to determine the relationship between toxicant exposure and PD incidence, morbidity and mortality using Cox proportional hazards regression with time-varying measures of chronic exposure, adjusting for confounding. Phase 2: Conduct a case-control study in a stratified random sample of cases and matched controls, collecting information on occupation, traumatic brain injury, and lifestyle risk factor information and conducting exams. Relevance: This work can help identify the causes and, ultimately, ways to prevent PD.						
<b>15. SUBJECT TERMS</b> Parkinson's disease, gene-environment, toxicants, registry, morbidity, mortality, geocode						
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## 1. INTRODUCTION:

This proposal investigates the association between Parkinson's disease (PD) risk and residential exposure to environmental toxicants in Santa Clara County, California (SCC). We will leverage our ongoing work that developed the legally-mandated Santa Clara County Parkinson's Disease Registry (SCCPDR) (AB 2248), identifying every SCC resident with PD with funding from USAMRAA W81XWH-07-1-0261 (a TATRC managed NETRP Program). We identified over 2200 PD cases prevalent in 2007, and continue to accrue incident cases. In the current project we will collect lifetime residential histories for PD cases and controls, and will link this data with unique and powerful time- and location-specific toxicant databases developed by the State of California over the past 50 years, in order to estimate cumulative toxicant exposures. We will test hypotheses that PD risk and PD-related morbidity and mortality are greater in persons exposed to pesticides, solvents, PCBs, and air pollutants. In addition, we will conduct a case control study in a stratified random sample of matched case and control subjects in whom we will conduct neurological examinations, collect detailed lifetime risk factor data (including history of traumatic brain injury), and collect blood and/or saliva for testing hypotheses of gene-environment interaction and for future hypothesis testing.

**2. KEYWORDS:** Parkinson's disease, gene-environment, toxicants, registry, morbidity, mortality, geocode

## 3. ACCOMPLISHMENTS:

### What were the major goals of the project?

YEAR 1: Establish study team; Approvals

- Develop study databases, data security and quality assurance methods (75% complete)
- Convene study investigator team, establish regular team meetings, finalize study protocol (90% complete)
- Train all research staff (75% complete)
- Obtain USAMRMC ORP HRPO approval (completed)

YEARS 1-2: Determine if risk of PD is increased in persons exposed to specific environmental toxicants. )

- Identify all cases of PD in SCC
  - PD case-finding. Continue active surveillance for PD diagnoses using methods developed under USAMRAA W81XWH-07-1-0261. (80% complete)
  - Control subject identification. Controls will be identified from all SCC residents, frequency matched to incident PD cases on age, gender and duration of SCC residence. A sufficient number of controls will be contacted in order to match cases at a 1:1 ratio. (*Control identification and recruitment methods are under development*)
  - Determine lifelong residential addresses. a) All subjects will be mailed a questionnaire requesting lifelong address information; b) For non-respondents, we will use a commercial service. (*Questionnaire complete; web-based questionnaire 80% complete*)
  - Determine key covariate information and, for cases, disease features. The mailed questionnaire will include brief, validated self-report questions to collect critical covariate and PD specific information. (*Questionnaire complete*)
  - Geocode addresses using California Environmental Health Tracking Program (CEHTP) expertise. (*Methods under development*)
  - Environmental toxicant data. With CEHTP, assess SCC toxicants spatially and temporally using multiple database sources. (*Methods under development*)
  - GIS-Exposure modeling. CEHTP will link residential and toxicant data; cumulative exposures for each subject will be determined. (*Methods under development*)

- Determine if morbidity or mortality is increased in PD cases exposed to environmental toxicants. (has not begun; pending full implementation of study Phase 1)
  - Death will be determined through annual searches of CA death certificate data obtained through the Vital Statistics Advisory Committee, as well as through searches of the National Death Index
  - Dementia, falls and fall-related morbidity will be determined from review of health utilization records, direct chart abstraction and, as possible, linkage with other CDPH databases

YEARS 2-3: Investigate the role of gene-environment interaction in the risk of PD, morbidity and mortality. (has not begun; pending full implementation of study Phase 1)

- Identify and enroll 200 case and 200 control subjects using stratified random sampling
- Conduct in-person clinical and risk-factor assessments, including history of traumatic brain injury
- Draw blood and extract DNA for genetic analysis
- Analyze DNA for genetic risk variants
- Bank blood for future analyses

YEAR 3: Analysis and Reporting (has not begun)

- Data analysis: toxicant x PD; toxicant x morbidity/mortality; gene-environment interaction
- Prepare results for publication

### **What was accomplished under these goals?**

- The project was transferred to the Northern California Institute for Research and Education at the San Francisco Veterans Affairs Medical Center effective 15 July 2014.
- Develop study databases, data security and quality assurance methods: We have established a preliminary study database. We continue to make modifications to refine the study databases and quality assurance methods.
- Convene study investigator team, establish regular team meetings, and finalize study protocol: We have established the study investigator team and convened the initial team meeting on 27-Aug-2013. Our internal team meets at regular intervals. In consultation with experts at our new institution, we continue to develop approaches that will provide us with the capabilities to most efficiently and rigorously implement the study protocol and achieve study scientific aims.
- Train all research staff: Training of research staff will continue to be an ongoing progress.
- Obtain USAMRMC ORP HRPO approval. Approval was obtained 9Sept2015:  
Overall Regulatory Status: *This study was initially approved by the Committee for the Protection of Human Subjects (CPHS) through the State of California Health and Human Services Agency on 20-June-2011 as a minimal risk study. Because we had not obtained funding, the study was never started and no subjects were enrolled.*
  - CHR initial review: *After transferring institutions, our IRB of record is the Committee for Human Research (CHR) at the University of California, San Francisco. A submission package to CHR was submitted on 11/10/14. We received pre-review changes back from CHR on 11/20/2014. We made the requested modifications and resubmitted the application to CHR on 12/5/2014. We received a CHR response to our submission package on 2/19/15. We submitted our response to CHR on 2/20/2015. We received CHR approval for the initial protocol and study instruments on 2/26/2015.*
  - VA Research and Development Committee (R&DC): *After submitting to CHR, our submission was reviewed both by CHR as noted above and also by the VA R&DC. On 1/24/2015 we received a memo from the VA Clinical Workshop Committee outlining the changes being requested by the R&DC. We responded to these changes by submitting a modification to our protocol on 3/26/2015. We received approval for the initial protocol and study instruments from the VA R&DC on 23April2015.*

- USAMRMC ORP HRPO: We spoke with Ms. Brigit Ciccarello on 17March2015 regarding our regulatory status. We sent Ms. Ciccarello all applicable documents for our HRPO submission on 19March2015. Ms. Ciccarello submitted these documents on our behalf to HRPO on 20March2015. We were assigned an HRPO analyst on 24March2015. We received questions from the HRPO analyst on 31March2015. We responded to these questions on 2April2015. On 8May2015 we received an email from Ms. Eaton at HRPO stating that no revisions were requested at this time. It was recommended that we submit documents currently approved by CHR to CPHS for review and approval.
- CPHS: Based on feedback from Ms. Eaton, we submitted an amendment on 2June 2015 to the protocol and documents to CPHS in order to match the CHR-approved protocol and study documents. We received comments back from CPHS on 15June2015. We resubmitted a revised application on 14 Jul 2015 in response to comments. We received approval for the revised application on 17 Jul 2015.
- Upon approval from CPHS, we resubmitted the revised documents to CHR for re-review on 5 Aug 2015. We received approval from CHR on 18 Aug 2015.
- The revised application approved by both CPHS and CHR was submitted on 31 Aug 2015 to Karen Eaton, Human Subjects Protection Scientist at HRPO-ORP. We received the HRPO approval memorandum on 9Sept2015.
- Continuing Review was submitted to CPHS on 15Dec2015 and we received approval on 5Feb2016.
- Continuing Review was submitted to CHR on 12Jan2015 and we received approval on 28Jan2016.
- Continuing Review was submitted to USAMRMS ORP HRPO on 8March2016.
- PD case-finding: Case rectification and de-duplication are ongoing.
- Control subject identification: Control identification and recruitment methods are under development.
- Determine lifelong residential addresses: The residential questionnaire has been finalized. Mailing of questionnaires will commence shortly. The questionnaire is additionally in the process of being converted to a web-based format that may be preferable to some subjects.
- Determine key covariate information and, for cases, disease features: Key covariate information will be collected as part of the residential questionnaire. This content has been developed.
- Geocode addresses using California Environmental Health Tracking Program (CEHTP) expertise. Methods for geocoding are under development with our collaborators in the CA Department of Health.
- Environmental toxicant data: Methods for toxicant assessments are under development with our collaborators in the CA Department of Health.
- GIS-Exposure modeling: Methods for linkage are under development with our collaborators in the CA Department of Health.

**What opportunities for training and professional development has the project provided?**

Nothing to Report.

**How were the results disseminated to communities of interest?**

Nothing to Report

**What do you plan to do during the next reporting period to accomplish the goals?**

Plans and milestones for the next quarter do not deviate from the original approved SOW.

- We will continue to refine the study database and develop data security and quality assurance methods as necessary.
- Continue to convene regular team meetings and continue to train all research staff.
- Determine lifelong residential addresses.

- Determine key covariate information and, for cases, disease features.
- Geocode addresses using California Environmental Health Tracking Program (CEHTP) expertise. Environmental toxicant data. With CEHTP, assess SCC toxicants spatially and temporally using multiple database sources.
- GIS-Exposure modeling. CEHTP will link residential and toxicant data; cumulative exposures for each subject will be determined.

#### **4. IMPACT:**

**What was the impact on the development of the principal discipline(s) of the project?**

Nothing to Report

**What was the impact on other disciplines?**

Nothing to Report

**What was the impact on technology transfer?**

Nothing to Report

**What was the impact on society beyond science and technology?**

Nothing to Report

#### **5. CHANGES/PROBLEMS:**

**Changes in approach and reasons for change**

Nothing to Report

**Actual or anticipated problems or delays and actions or plans to resolve them**

The change of institutions and the requirement for review by multiple human subjects review committees resulted in time delays in study initiation. Therefore, the Period of Performance at NCIRE was revised to terminate on March 31<sup>st</sup>, 2017. We obtained USAMRMC ORP HRPO approval on 9Sept2015 and have begun Phase 1 of the study. Due to prior delays in study initiation, we anticipate that a no-cost extension will be necessary in order to achieve study aims.

**Changes that had a significant impact on expenditures**

Our expenditures in Year 2 are lower than anticipated due to administrative delays because of changes of Institution and time to go through regulatory steps to receive USAMRMC ORP HRPO approval. We anticipate that all funds not expended in Years 1 and 2 are needed to complete our work in future years.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report

#### **6. PRODUCTS:**

Nothing to Report

#### **7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

## What individuals have worked on the project?

**Name:** Caroline M. Tanner, MD, PhD

**Project Role:** Principal Investigator

**Nearest person month worked:** 1

**Contribution to Project:** Dr. Tanner oversees all aspects of the project study design. She has worked with experts at our new institution to develop approaches that will provide us with the capabilities to most efficiently and rigorously implement the study protocol and achieve study scientific aims. She has overseen the development of study databases, data security and quality assurance methods. She has led team meetings. She has overseen all aspects of the regulatory submissions as detailed above.

**Funding Support:** W81XWH-13-1-0054

**Name:** Samuel Goldman, MD, MPH

**Project Role:** Co-Investigator

**Nearest person month worked:** 2

**Contribution to Project:** Dr. Goldman has assisted Dr. Tanner in the oversight of all aspects of the project study design. He has developed study databases, data security and quality assurance methods and worked on all aspects of the regulatory submissions detailed above.

**Funding Support:** W81XWH-13-1-0054

**Name:** Kathleen Comyns

**Project Role:** Project Manager

**Nearest person month worked:** 3

**Contribution to Project:** Ms. Comyns has worked under Drs. Tanner and Goldman to assist in the development of study databases, data security and quality assurance methods. She has assisted in writing study progress reports. She has worked on all aspects of the regulatory submissions detailed above.

**Funding Support:** W81XWH-13-1-0054

## Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Tanner's Current Other Support:

### ACTIVE

Michael J. Fox Foundation  
A123626

4/22/2013-6/30/2016  
1% effort

0.12 calendar

#### *Bay Area Solvent Study - Symptoms (BASS-S)*

The goal of this work is to garner better understanding of the link between exposure to environmental toxins and prodromal and frank Parkinson's disease (PD).

Role: PI

Michael J. Fox Foundation  
A123349

4/1/2010-12/31/2016

0.6 calendar  
5% effort

#### *The Parkinson's Progression Markers Initiative (PPMI) Steering Committee Membership*

The goal of this steering committee membership is for members to take responsibility for the scientific rationale, study design, site selection, logistics, data management and analysis planning for the PPMI study.

Role: PI



calendar

A124459

1% effort *The Parkinson's**Progression Markers Initiative (PPMI)*

The goal of this project is to develop a comprehensive and uniformly acquired PD clinical and imaging dataset that can be used to identify and validate clinical, imaging and biomic biomarkers of progression and establish standardized protocols for acquisition, transfer and analysis of data.

Role: Site PI

PDF-PRV-1517

12/01/2014-05/31/2016

0.12 calendar

Parkinson's Disease Foundation (A124549)

1% effort

*Prevalence and Incidence of Parkinson's Disease in 4 California Counties 2008-10*

The goal of this project is to determine the incidence of Parkinson's disease in the four counties in the California Parkinson's Disease Registry pilot project.

Role: PI

Michael J. Fox Foundation

08/01/2015-07/31/2016

0.24 calendar

*FOUND in PPMI (A125779)*

1% effort

The goal of this project is to maintain contact with all PPMI participants using remote assessment methods.

Role: PI

UCSF Resource Allocation Program (PI: Goldman) 2/1/2016 – 7/31/2017

0.24 calendar

7504276

1% effort

*Parkinson's Disease Concordance and Heritability in the NAS/NRC World War II Veteran Twins Cohort*

This study will use National Death Index data to update our previously-derived PD concordance rates in monozygotic and dizygotic twins.

Role: Co-Investigator

R01ES020718 (PI: Greenamyre, U of Pittsburgh) 8/5/2014-5/31/2016

0.48

calendar

NIH/NIEHS

4% effort *MtDNA**Damage as a Biomarker for Environmental Mitochondrial Toxicity*

The goal of this project is to investigate mitochondrial toxicities from multiple environmental toxicants that have been associated in epidemiology studies with Parkinson's disease (PD).

Role: Subproject PI (Tanner Project)

R01ES020718 (PI: Greenamyre, U of Pittsburgh) 8/5/2014-5/31/2016

0.12 calendar

NIH/NIEHS

1% effort *MtDNA**Damage as a Biomarker for Environmental Mitochondrial Toxicity*

The goal of this project is to investigate mitochondrial toxicities from multiple environmental toxicants that have been associated in epidemiology studies with Parkinson's disease (PD).

Role: Subproject Co-investigator (Goldman Project)

R21 NIOSH (PI: Goldman)

9/1/2013-8/31/2016

0.12 calendar

NIOSH

1% effort

*Trichloroethylene and Parkinson's Disease*

The goal of this work is to identify occupational causes of Parkinson's disease (PD). This project will investigate the relationship of occupational exposure to the solvents trichloroethylene (TCE), tetrachloroethylene (PERC) and carbon tetrachloride (CCl<sub>4</sub>) and the risk of PD in two study populations. Role: Co-Investigator

**OVERLAP**

There are no scientific or budgetary overlaps between the funded grants listed above and the current proposal

**What other organizations were involved as partners?**

The subcontract with the Public Health Institute has been established. The subcontract with Kaiser Permanent Northern California will be established.

**8. APPENDICES:** None