AWARD NUMBER: W81XWH-18-1-0509

TITLE: Interactions of gut microbiome, genetic susceptibility and environmental factors in Parkinson's disease

PRINCIPAL INVESTIGATOR: David Standaert, MD, PhD

CONTRACTING ORGANIZATION: University of Alabama at Birmingham
Birmingham, AL 35294

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
David Standaert, MD, PhD

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University of Alabama at Birmingham
UAB
701 S 20th St
Birmingham, AL 35294-0001

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Genetic and environmental factors explain a fraction of Parkinson disease risk, prompting the question if microorganisms in the gut may be the trigger. The main goal of this proposal is to validate and investigate the mechanisms of interaction in a pre-clinical mouse model of PD. To do this, we will create a germ-free (experimental) and specific pathogen free (control) pre-clinical mouse model in which alpha-synuclein is constitutively expressed under the Thy1 promotor (Thy1-SNCA). In order to test whether pathogenic microorganisms present within the gut trigger PD-like pathology, we will transfer *corynebacteria* to germ free and specific pathogen free Thy1-SNCA mice and assay for exacerbated inflammation, striatal dopamine loss, behavioral deficits, and dopamine cell loss. During this research period, we have obtained, bred, and transferred Thy1-SNCA transgenic mice in both our traditional mouse colony and the gnotobiotic facility. We have also confirmed alpha-synuclein expression via PCR and protein expression in the brain of Thy1-SNCA mice via western blot. In the next cycle, we plan to expand/breed both germ free and specific pathogen free colonies of mice, as well as confirm germ free and specific pathogen free status via sequencing.

15. SUBJECT TERMS
Parkinson Disease, microbiome, mouse models, alpha-synuclein, gnotobiotic

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
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INTRODUCTION:

Genome-wide studies have identified 28 independent genetic risk variants for idiopathic Parkinson Disease (PD), but each has a small effect, and together, they account for a fraction of the genetic component in PD. Epidemiological studies have associated several elements with PD, most notably, exposure to herbicides/pesticides with increased risk, and cigarette smoking and caffeinated coffee consumption with reduced risk of PD, but as with genetic factors, individual effects are small. Many groups have tested interaction between the genetic and environmental risk factors of PD in hypotheses-driven studies, and we have conducted hypothesis-free genome-wide geneenvironment interaction studies. These studies discovered modifier genes with critical clues to PD pathogenesis, but they were unable to produce any gene-environment interactions that could explain PD risk completely. There must be more to gene-environment interaction in PD than the human genome and the environmental factors that we know of. This research program, awarded under the Partnering PI option, is based on preliminary data that indicates the gut microbiome is the missing link. Dr. Payami is the Initiating PI and will provide a separate progress report. This component of the project, led by the coordinating PI Dr. Standaert, encompasses Aim 5 of the overall proposal: To investigate the mechanisms of interactions. Hypothesis: Corynebacterium will increase alpha-synuclein and accelerate parkinsonian phenotypes in a mouse model. Rationale: Transplant of a PD microbiome has been shown to enhance parkinsonian phenotypes in alpha-synuclein over-expressing mice, but the responsible microorganisms are unknown. Research strategy: We will use Thy1-SNCA specific pathogen-free and germ-free mice and test the effect of introducing Corynebacterium on alpha-synuclein and relevant phenotypes.

1. **KEYWORDS**

   Parkinson Disease, microbiome, mouse models, alpha-synuclein, gnotobiotic

2. **ACCOMPLISHMENTS**

   What were the major goals of the project? The goals of this Partnering PI project are as described in the original Statement of Work, and are listed in the Table below.

Major Goals	**Timeline in months**	**% Complete**
Aim 5. Investigate the mechanisms of interactions in model organisms.		
Major Task 1: Re-deriving Thy1-SNCA mouse in gnotobiotic facility and breeding of SPF mice		
Subtask 1: Re-derive Thy1-SNCA mouse in gnotobiotic facility	1-12	90%
Subtask 2: Breeding of GF Thy1-SNCA mouse in gnotobiotic facility	6-24	0
Subtask 3: Breeding of SPF Thy1-SNCA mouse in conventional housing facility	1-24	90%
Major Task 2: Transfer of Corynebacterium to SPF and GF mice for 1 month time point		
Subtask 1: Transfer of Corynebacterium to SPF and GFP mice	12-24	0
Subtask 2: Confirmation of stable Corynebacterium infection by fecal PCR	12-24	0
Subtask 3: Collection of tissues for 1 month analysis	24-36	0
Subtask 4: 1 month data collection/analysis	24-36	0
Major Task 3: Transfer of Corynebacterium to SPF and GF mice for 6 month time point		
Subtask 1: Transfer of Corynebacterium to SPF and GFP mice	24-36	0
Subtask 2: Collection of tissues for 6 month analysis	36-48	0
Subtask 3: 6 month data collection/analysis	36-48	0
Milestone #6: Co-author manuscript on Corynebacterium in Thy1-SNCA mouse model of PD	48	

What was accomplished under these goals?

During this one year reporting period, we have:

1. Successfully executed a Materials Transfer Agreement with the University of California, San Diego (UCSD), the source of the mouse line required for these studies.
2. Obtained Thy1-aSyn (SNCA) transgenic mice from UCSD. A total of 5 female mice were received.
3. Established a genotyping protocol to identify the transgenic animals. With the collaboration of UCSD investigators, we purchased appropriate DNA primers and established a PCR assay to detect the presence of the transgene (Figure 1, below).

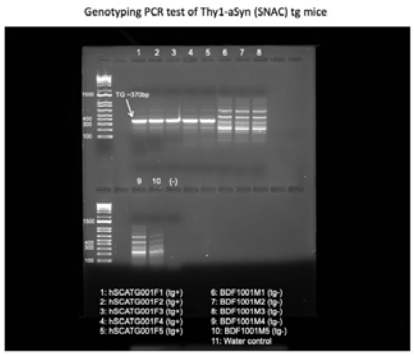


Figure 1. PCR assay for presence of the alpha-synuclein transgene. Lanes 1-5 contain DNA from the transgenic mice provide by UCLA, while 6-10 contain DNA from control mice. The presence of the

4. Established breeding of the transgenic animals in a standard mouse housing facility.
5. In order to validate the mouse line, we designed two pairs of PCR primers spanning the transgene (Figure 2) and sequenced the PCR products covering the whole hSNCA transgene and neighboring regions (Figure 3). We confirmed that the transgenes of original 4 breeder females are of the correct sequence, an important authentication of the animals.

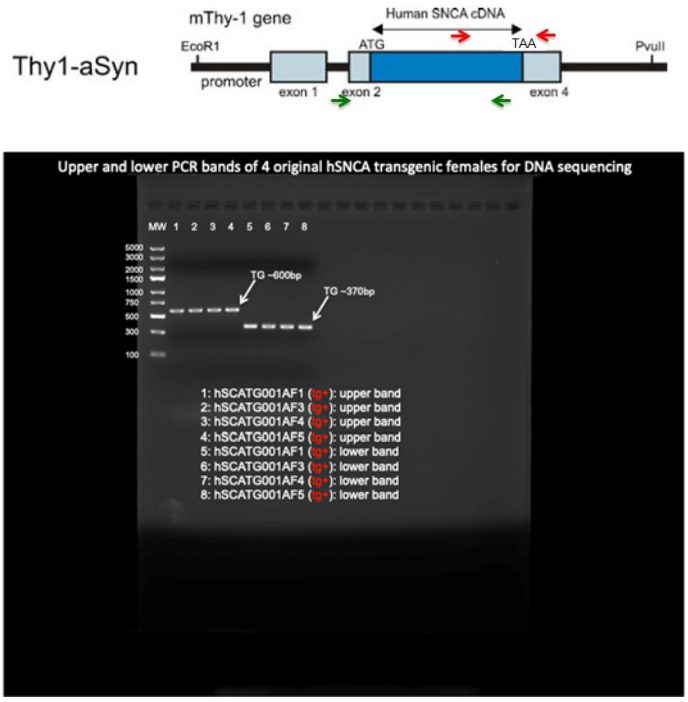


Figure 2. Validation that the hSNCA transgene sequence of the original female breeders is correct. Top illustrates design of a pair of primers specific to an upper region of hSNCA transgene. Lower panel illustrates PCR amplification of upper and lower PCR fragments of hSNCA transgene.

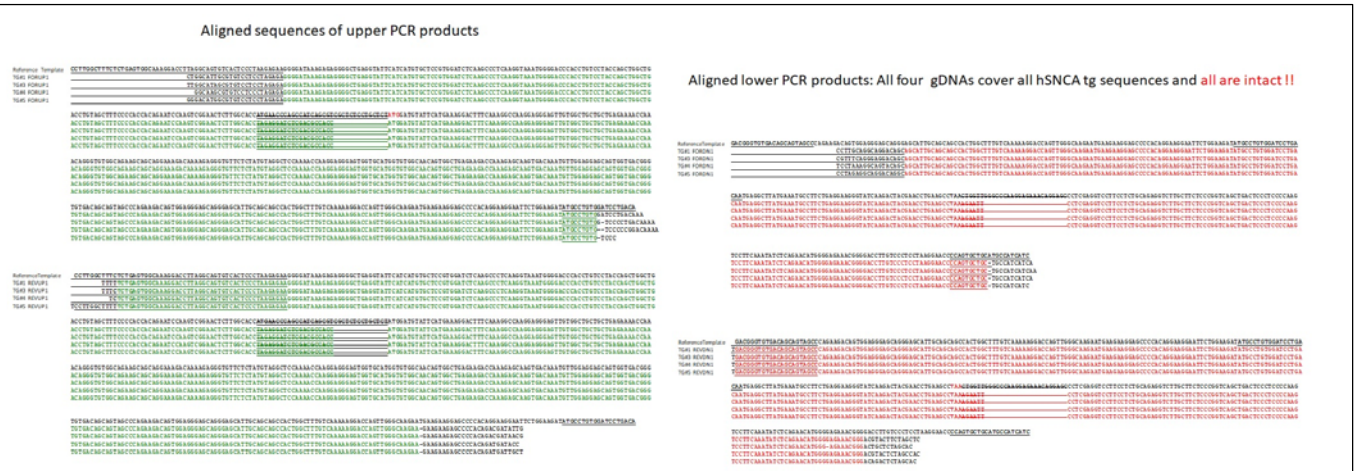


Figure 3. Sequence alignment of 4 original female breeders by Sanger DNA sequencing with SNCA reference sequence. This demonstrates that the transgene in each animal matches the human SNCA reference sequence.

6. Established breeding of the transgenic animals in a standard mouse housing facility. We have successfully obtained twenty-seven litters of pups derived from our five female founders. Of the pups genotyped so far, 55 are transgene positive. These animals are currently aging for our study.

7. We have successfully completed an alpha-synuclein selective western blot to confirm transgene expression in the cortex (CTX), ventral midbrain (MB), and cerebellum (CB) in the transgenic positive animals (Figure 4). Anti-vinculin was blotted as a loading control.

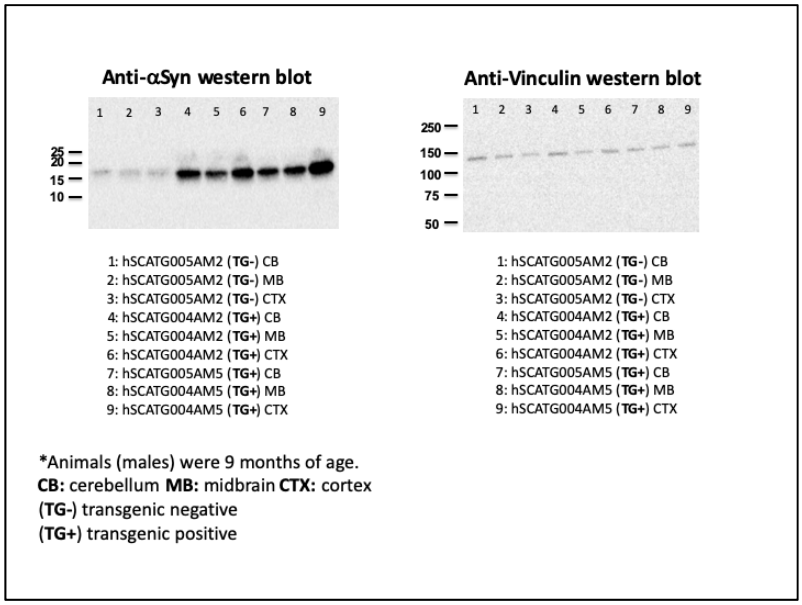


Figure 4: Western blot detecting the overexpression of alpha-synuclein in the cerebellum, ventral midbrain, and cortex of 9 month old transgenic positive (TG+) animals. Anti-vinculin was blotted in the same samples as a loading control.

8. We established 30 breeding pairs of transgenic animals and non-transgenic control animals, and have transferred the pregnant females to the UAB germ-free core facility. At this time, we have derived 3 transgenic germ-free females, and 9 non-transgenic control breeders. Both are currently fostered within the facilty and will be ready for breeding in 8 weeks pending verification of germ-free status.

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?

1) Further expand and/or maintain the number of animals in the specific pathogen free breeding colony. We also plan to confirm the "specific pathogen free" status by sequencing.
2) Confirm the germ-free status of the 3 TG+ females and the 9 NTG control pups in the gnotobiotic facilty.
3) Further expand the TG+ and NTG germ-free colonies in the gnotobiotic facilty.
4) Re-derive additional TG+ and NTG animals for successful breeding if necessary.

3. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*
    - **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*
4. **CHANGES/PROBLEMS:**
    - **Changes in approach and reasons for change**
        - *The project is proceeding as planned. No changes to report.*
    - **Actual or anticipated problems or delays and actions or plans to resolve them**
        - *We do not anticipate any delays to the schedule at this point.*
    - **Changes that had a significant impact on expenditures**
        - *Nothing to report*
    - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
        - *Nothing to report*
5. **PRODUCTS:**
    - **Publications, conference papers, and presentations**
      Nothing to report

- **Website(s) or other Internet site(s)**
  Nothing to report
- **Technologies or techniques**
  Nothing to report
- **Inventions, patent applications, and/or licenses**
  Nothing to report
- **Other Products**
  Nothing to report

6. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

What individuals have worked on the project?

Name: David Standaert, MD, PhD
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-2921-8348
Nearest person month worked: 0.6 CM (for year), 5% for 12 months
Contribution to Project: Dr. Standaert oversaw the project start up, meeting with project personnel to design, implement, and troubleshoot initial experiments.

Name: Ashley Harms, PhD
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0002-7054-2812
Nearest person month worked: 2.04 CM (for year), 17% for 12 months
Contribution to Project: Dr. Harms managed the day to day operation of the project and supervised the Research Associate assigned to this project.

Name: Woong-Jai Won
Project Role: Research Associate
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 4.32 CM (for year), 36% for 12 months
Contribution to Project: Dr. Won has been responsible for monitoring animal care and breeding, collecting tail DNA, extracting DNA, developing and performing the genotyping assay.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - There have been changes in the active other support for Dr. Standaert and Dr. Harms. Please see attached Other Support documents with changes highlighted.
- **What other organizations were involved as partners?**
  - Nothing to report

7. **SPECIAL REPORTING REQUIREMENTS**
   - **COLLABORATIVE AWARDS:**
     - This report encompasses reporting for the Collaborating PI of the this award. The Initiating PI, Dr. Haydeh Payami, will submit a separate report.

8. **APPENDICES:**
    - There are no appendix materials.

Current/Pending/Previous Support

David Standaert

Current Support, continuing since last reporting

Title: Molecular Etiology of Early Onset Dystonia (P01NS087997)
Role: Co-Investigator
Time Commitment: 4%
Support Agency: National Institutes of Health, pass through Massachusetts General Hospital
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 7/1/15 – 6/30/20
Annual Direct Costs: $186,975
Project Goals: This project explores cholinergic and dopaminergic mechanisms in mouse models of dystonia.
Specific Aims:
Hypothesis 1: Defects in THAP1 (DYT6) and deficiency of the Gαolf regulatory G protein (DYT25) produce abnormalities in cholinergic transmission and downstream signaling similar to those observed in DYT1 dystonia models.

Aim 1a. Using in vitro slice electrophysiology, evaluate the membrane properties of striatal cholinergic interneurons and their response to muscarinic and dopaminergic agonists and antagonists in THAP1 C54Y mutation knock-in and Gαolf heterozygous knock-out mice.

Aim 1b. Using in vitro slice preparations, evaluate striatal long-term synaptic depression (LTD) and the effects of muscarinic antagonists, D2 receptor agonists and A2a receptor antagonists on striatal plasticity in THAP1 C54Y mutation knock-in and Gαolf heterozygous knock-out mice.

Aim 1c. Using in vitro slice preparations, evaluate the role of downstream signaling pathways (identified by Projects 1 and 2) on the properties of cholinergic and striatal medium spiny neurons in these models.

Hypothesis 2: Cholinergic dysfunction in dystonia and disruption of downstream signaling leads to abnormal regulation of striatal dopamine release.

Aim 2a. Using in vivo microdialysis in the knock-in model of DYT1 dystonia, determine whether muscarinic
or nicotinic inhibitors of cholinergic receptors can normalize amphetamine-stimulated dopamine release.

Aim 2b. Using in vivo microdialysis, evaluate the effect of amphetamine on striatal dopamine release in THAP1 C54Y mutation knock-in and Gαolf heterozygous knock-out animals, and the modulation of dopamine release by muscarinic and nicotinic receptors.

Aim 2c. Using in vivo microdialysis, evaluate the modulation of dopamine release in these models by downstream signaling pathways (identified by Projects 1 and 2) in cholinergic and dopaminergic neurons.

Hypothesis 3: Subtype selective muscarinic antagonists and modulators can reverse abnormalities in striatal dopamine release plasticity and motor function in DYT1, THAP1, and GNAL models of dystonia.

Aim 3a. Determine the effects of selective muscarinic antagonists and allosteric modulators on the electrophysiological properties of cholinergic neurons and on striatal plasticity in slice preparations from DYT1, THAP1, and GNAL mouse models in vitro.

Aim 3b. Determine the effects of selective muscarinic antagonists and allosteric modulators, delivered by reverse dialysis, on striatal dopamine release in DYT1, THAP1, and GNAL mouse models in vivo.

Aim 3c. Determine the effect of a selective M1 antagonist (VU0255035) and a selective M4 positive allosteric modulator (VU0152100) on motor phenotypes in DYT1, THAP1 and GNAL models.

Potential Overlap: None.

Title: APDA Advanced Center for Parkinson's Research

Role: PI
Time Commitment: 1%
Support Agency: American Parkinson's Disease Association
Funding Agency Grants officer:
Leslie A. Chambers
Parkinson Plaza
135 Parkinson Ave
Staten Island, NY 10305
Performance Period: 9/1/06-8/31/20
Annual Direct Costs: $120,000
Project Goals: The APDA advanced center supports pilot and investigational projects in Parkinson's disease.
Potential Overlap: None.

Title: The Parkinson's Progression Markers Initiative (PPMI)
Role: Site PI
Time Commitment: 5%
Support Agency: The Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Todd Sherer
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 7/27/10 – 12/31/23 extension
Total Direct Costs: $1,779,939
Project Goals: The primary objective of this study is to identify clinical, imaging and biologic markers of PD progression for use in clinical trials of disease-modifying therapies.
Specific Aims:
Aim 1: Establish standardized protocols for acquisition, transfer and analysis of clinical, imaging and biomic data that can be used by the PD research community.++
Aim 2: Develop a comprehensive and uniformly acquired clinical and imaging dataset and biological samples that can be used to estimate the mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in early PD patients.
Aim 3: Investigate existing and identify novel clinical, imaging and biomic Parkinson disease progression markers to identify quantitative individual measures or combination of measures that demonstrate optimum interval change in PD patients in comparison to healthy controls or in sub-sets of PD patients defined by baseline assessments, progression milestones and/or rate of clinical, imaging or biomic change.
Aim 4: Conduct preliminary verification studies on promising biological markers using stored collected samples.
Potential Overlap: None.

Title: UAB Cannabidiol Program
Role: PI
Time Commitment: 10%
Support Agency: Alabama Department of Commerce
Funding Agency Grants officer:
Angela Till
401 Adams Ave
PO Box 304106
Montgomery, AL 36130
Performance Period: 4/1/14 – 6/30/22 extension
Total Direct Costs: $5,000,000

Project Goals: The goal of this program is to establish a research study which will provide access to cannabidiol for epileptic conditions and gather data on outcomes in both adults and children.
Potential Overlap: None.

Title: National Resource Center for High-Impact Clinical Trials in Medical Rehabilitation (P2CHD086851)
Role: Executive Committee, Pilot Projects Associate Director
Time Commitment: 2%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Ralph Nitkin
BG 6710B RM 2116
6710B Rockledge Dr
Bethesda, MD 20817
Performance Period: 9/17/15 – 6/30/20
Annual Direct Costs: $202,763
Project Goals: The goal of this project is to catalyze high-impact, interdisciplinary clinical trials nationally that will: (i) reveal fundamental underpinnings; (ii) define optimal intervention strategies; and (iii) streamline translation to clinical and community-based application.
Aim 1: To advance the research of medical rehabilitation investigators nationally, we will provide effective consultative and/or educational services and collaborative arrangements that will facilitate all aspects of clinical trial design ad conduct, and competitive funding will be awarded nationally for innovative pilot projects needed to shape large-scale, definitive clinical trials (e.g., dosing trials, adaptive, delayed start, withdrawal and futility trials, and trials evaluating the interactions of complex mixtures of treatment modalities, etc.).
Aim 2: To encourage medical rehabilitation researchers to take full advantage of the national resource Center's unique resources and expertise by effectively promoting and disseminating all of the Center's programs.
Aim 3: To develop, validate, and provide state-of-the-art techniques and tools that will strengthen high-impact clinical trials nationally by enabling medical rehabilitation researchers to conduct more rigorous trials yielding higher quality data with potentially greater influence on clinical practice and health care deliver.
Potential Overlap: None.

Title: UAB Neuroscience Core Center – Core B: Molecular Detection and Stereology Core (P30NS047466)
Role: Core Leader
Time Commitment: 5%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Randall Stewart
NSC BG RM 2135
6001 Executive Blvd
Rockville, MD 20852
Performance Period: 8/1/16 – 5/31/20
Annual Direct Costs: $107,420
Project Goals: The major goal of this grant is to provide core support services for a highly productive group of 19 NINDS-funded investigators and their neuroscience research activities. The proposed cores are designed in response to investigators inputs and will promote better science, reduce costs to individual investigators and increase productivity. The goal is to enhance the research environment by providing high quality research core support services within a scientifically stimulating multidisciplinary setting.
Specific Aims:
Aim 1: Provide cost-effective, reproducible, high-throughput ISH and IHC detection on “routine” specimens.
Aim 2: Assist investigators in the development and implementation of advanced detection techniques including multi-label IHC, dual label ISH/IHC, ultrasensitive TSA Plus detection and quantum dot labeling procedures.
Aim 3: Assist users in the performance of precise, unbiased state-of-the-art stereologic/morphometric image analysis of histological preparations.

Potential Overlap: None.

Title: DUOdopa/Duopa in Patients with Advanced Parkinson's Disease (PD) – A Global Observational Study Evaluating Long-Term Effectiveness (DUOGLOBE)
Role: Site Investigator
Time Commitment: 1%
Support Agency: AbbVie, Inc
Funding Agency Grants officer:
Lars Bergmann, MD
Global Medical Director
Global Medical Affairs Neuroscience
AbbVie Europe
10, rue d'arcueil
94150, Rungis
France
Performance Period: 2/8/16 – 2/7/21 extension
Total Direct Costs: $67,000
Project Goals: The primary objective of this post-marketing observational study (PMOS) is to assess the effectiveness of LCIG treatment on OFF time as reported by the patient at scheduled visits from baseline to 36 months in advanced Parkinson's disease patients who are treated in accordance with the approved local product label and reimbursement criteria under the conditions of routine clinical care.
Potential Overlap: None.

Title: UAB Research and Education Program in Neuroscience
Role: PI
Time Commitment: 3%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Stephen J. Korn
NSC BG RM 2187
6001 Executive Blvd
Rockville, MD 20852
Performance Period: 7/1/17 – 6/30/22
Annual Direct Costs: $202,912
Project Goals: The goal of this education program is to train residents in neuroscience for careers as physician-scientists.
Specific Aims: The Specific Aim of this proposal is to establish an R25 education program at UAB to train residents in neurology, neurosurgery, radiology, anesthesiology and neuropathology, and to prepare them for careers as physician-scientists. The program will incorporate leadership from two clinician-scientists who will serve as Director and Associate Director, a group of experienced mentors, and strong residencies programs from which candidates will be drawn. Several potential initial candidates are proposed.
Potential Overlap: None.

Title: MJFF Emerging Targets Committee Membership
Role: PI
Time Commitment: 1%
Support Agency: The Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Todd Sherer
Grand Central Station
PO Box 4777
New York, NY 10163-4777

Performance Period: 6/1/16 – 6/30/20
Total Direct Costs: $3,200
Project Goals: The goal of this committee is to advise the MJFF on its Emerging Target initiatives, focused on identifying and assessing novel therapeutics approaches for Parkinson's patients.
Potential Overlap: None.

Current Support, new since the last reporting

Title: Interactions of Gut Microbiome, Genetic Susceptibility and Environmental Factors in Parkinson's Disease (W81XWH1810509)
Role: PI
Time Commitment: 5%
Support Agency: Department of Defense
Funding Agency Grants officer:
Jason Kuhns
Performance Period: 9/1/18 – 8/31/22
Annual Direct Costs: $103,195
Project Goals: The goal of this study is to identify the organisms in the gut that interact with genetic and environmental risk factors of PD. Microbiome can be easily altered; thus, successful completion of this project will provide feasible means to predict, prevent and treat PD.
Specific Aims:
Aim 5. Investigate the mechanisms of interactions. Hypothesis: Corynebacterium will increase alpha-synuclein and accelerate parkinsonian phenotypes in a mouse model. Rationale: Transplant of a PD microbiome has been shown to enhance parkinsonian phenotypes in alpha-synuclein over-expressing mice,24 but the responsible microorganims are unknown. Approach: We will use Thy1-SNCA specific pathogen free and germ-free mice and test the effect of introducing Corynebacterium on alpha-synuclein and relevant phenotypes.
Potential Overlap: None.

Title: Innate and Adaptive Immunity in Parkinson Disease: Core A – Administrative Core; (P50NS108675)
Role: PI
Time Commitment: 8%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 9/30/18 – 7/31/23
Annual Direct Costs: $78,004
Project Goals: The primary mission of the Administrative Core is to promote the integration and function of the Udall Center components and activities, and provide the infrastructure required for Center communication, decision-making and administration and the activities of the Program Director.
Specific Aims:
Aim 1: Promote the integration and function of the Alabama Udall Center components and activities, and provide the infrastructure required for Center communication, decision-making and administration and the activities of the Program Director.
Aim 2: Support and organize periodic meetings of the Center Executive Committee, project staff, Internal Advisory Committee, External Advisory Committee, and collaborators.
Aim 3: Coordinate activities that fulfill the Alabama Udall Center Mission Statement for Training: "Training for physicians, scientists and the community today to accelerate progress in PD research and treatment, and

education to develop the scientific workforce and community partnerships of the future."
Aim 4: Enhance the integration of the Alabama Udall Center with UAB internal Parkinson disease research programs.
Aim 5: Promote the integration of the Alabama Udall Center with other Udall Centers and national programs in PD research
Aim 6: Develop and conduct outreach activities for the local and national Parkinson community, including an annual Alabama Udall Center symposium to present research results to the local community.
Aim 7: Coordinate interactions of the Alabama Udall Center with NINDS staff, including providing advance notice of manuscripts and publications to the NINDS program officer and working with the NINDS Office of Communications and Public Liaison on press releases highlighting Center accomplishments.
Aim 8: Organize an annual retreat of the Alabama Udall Center investigators, Internal Advisory Committee, collaborators, and other investigators in related areas. This will also include an annual evaluation of the Alabama Udall Center progress and directions by the External Advisory Committee.
Aim 9: Maintain an accounting of resource generation and related utilization, and steps taken to maximize the research utilization of these resources within and beyond the Alabama Udall Center. Coordinate data and resource sharing both between Alabama Udall Center investigators and with other Udall Centers and outside investigators and organizations.
Aim 10: Ensure that all components of the Alabama Udall Center maintain compliance with NIH policy requirements.
Aim 11: Prepare and submit annual progress reports for the Alabama Udall Center.
Aim 12: Support the Alabama Udall Center web site and social media outreach.
Aim 13: Coordinate attendance of the Center Director, Center Administrator, and Project and Core Leads at the annual Udall Centers meeting.
Potential Overlap: None.

(Approved for funding, award pending)
Title: Innate and Adaptive Immunity in Parkinson Disease: Project 1 - Role of Innate Immune Cells in Human Parkinson Disease (P50NS108675)
Role: Project Leader
Time Commitment: 15%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 9/30/18 – 7/31/23
Annual Direct Costs: $191,409
Project Goals: The goal of this project is to explore the overarching hypothesis that innate immune cells are activated towards a pro-inflammatory phenotype early in PD. We theorize that blocking this activation will protect from PD progression.
Specific Aims:
Aim 1: In the same population of 60 patients with de novo PD and 60 age- and sex-matched controls, determine whether there is change over time in monocytes populations assessed by flow cytometry or in blood cytokines and chemokines.
Aim 2: Determine the relationship between baseline measures of inflammation and longitudinal clinical outcomes, particularly cognition, in this population of early de novo PD subjects.

Title: A 52-Week, Open-Label, Single-Arm Study to Evaluate The Safety and Tolerability of 24-hour Daily Exposure of Continuous Subcutaneous Infusion of ABBV-951 in Subjects with Parkinson's Disease
Role: Site Investigator
Time Commitment: 5%

Support Agency: AbbVie, Inc
Funding Agency Grants officer:
Edward Buell
Associate Director, Abbvie Inc.
Performance Period: 8/27/19 – 8/26/24
Total Direct Costs: $453,344
Project Goals: The primary objective of this study is to assess the local and systemic safety and tolerability of ABBV-951 delivered as a CSCI for 24hours daily for up to 52 weeks.
Potential Overlap: None.

Pending Support

None.

Previous Support, ended since last reporting

Title: UAB Bachmann-Straus Dystonia and Parkinson's Disease Center of Excellence
Role: PI
Time Commitment: 1%
Support Agency: The Bachmann-Strauss Dystonia & Parkinson Foundation, Inc.
Funding Agency Grants officer:
Todd Sherer
Grand Central Station
P.O. Box 4777
New York, NY 10163-4777
Performance Period: 09/15/13 – 09/14/18
Annual Direct Costs: No cost extension
Project Goals: This program establishes a Center of Excellence with the mission of integrating the elements of research and clinical care for patients with dystonia and Parkinson's disease, and it supports pilot research projects in dystonia.
Specific Aims:
Aim 1: To establish a clinical center of excellence, which will provide patients with an integrated approach to multi-disciplinary care for dystonia and Parkinson disease. This will include community outreach, coordination of care, and facilitation of access to multidisciplinary treatment including movement disorder specialists, physical, occupational and speech therapy, botulinum toxin treatment, neurosurgical treatment, and genetic counseling.
Aim 2: To enhance the access of patients to clinical trials in dystonia and Parkinson disease, and enable conduct of trials which will advance the fields.
Aim 3: To facilitate the interactions between clinicians, basic scientists, and members of the community, and promote cross-culture efforts to translate new discoveries.
Aim 4: To train the next generation of dystonia and Parkinson disease clinicians and scientists, through support of clinical and basic/translational fellowships.
Potential Overlap: None.

Title: 18F-AV-1451-A09: 18F-AV-1451 Injection for Brain Imaging of Tau in Subjects with Progressive Supranuclear Palsy (PSP), Subjects with Corticobasal Degeneration (CBD) and Healthy Volunteers
Role: Sub-investigator (backup)
Time Commitment: 0.1%
Support Agency: Avid Radiopharmaceuticals
Funding Agency Grants officer:

Sean R. Doyle, MSc
Clinical Research Associate II
Avid Radiopharmaceuticals
3711 Market Street, Suite 710
Philadelphia, PA 19104
Performance Period: 8/7/14 – 8/6/18
Total Direct Costs: $104,512
Project Goals: The major goal of this study is to determine the pattern of tau deposition in PSP using AV-1451 PET imaging.
Specific Aims:
Aim 1: To conduct a preliminary evaluation of 18F-AV-1451 for brain imaging of tau in subjects with progressive supranuclear palsy (PSP), subjects with corticobasal degeneration (CBD) and healthy volunteers.
Aim 2: To obtain information regarding the safety of 18F-AV-1451 in these populations. Exploratory objectives include:

1. To correlate 18F-AV-1451 imaging with clinical features of PSP and CBD; and
2. To evaluate change in 18F-AV-1451 imaging over 9 months in PSP and CBD subjects.

Potential Overlap: None.

Title: Causes, Treatment, and Prevention of Corticobasal Degeneration
Role: Sub-investigator (backup)
Time Commitment: 0.01 calendar months
Support Agency: University of California, San Francisco
Funding Agency Grants officer:
Adam Boxer, M.D., Ph.D.
UCSF Memory and Aging Center
675 Nelson Rising Lane, Box 1207
San Francisco, CA 94158
Performance Period: 7/1/14 – 9/30/18
Annual Direct Costs: $30,242 (subaward to UAB)
Project Goals: The major goal of this study is to determine the efficacy of a new microtubule stabilizing drug in 4R tauopathies.
Specific Aims:
Aim 1: To determine the safety and tolerability [maximum tolerated dose (MTD) within planned dosing range] of intravenous (IV) infusions of TPI 287 administered once every 3 weeks for 9 weeks (for a total of 4 infusions) in patients with primary four repeat tauopathies (4RT), corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP).
Aim 2: To determine the pharmacokinetic (PK) profile of TPI 287 in plasma after a single IV infusion of TPI 287 and the steady-state cerebrospinal (CSF) concentration of TPI 287 1 week after completion of the fourth infusion.
Potential Overlap: None.

Previous Support, no change since last reporting

Title: BTK Inhibitors and Their Potential Role in Inhibiting the Pro-Inflammatory Microenvironment Associated with Neurodegeneration
Role: PI
Time Commitment: 2%
Support Agency: Acerta Pharma B.V.
Funding Agency Grants officer:
Cecile Krejsa, PhD
15400 SE 30th Place Suite 206,
Bellevue, WA 98007
Performance Period: 1/1/15 – 12/5/16

Annual Direct Costs: $100,679
Project Goals: The goal of this project is to evaluate whether the administration of ACP-196 can reduce the pro-inflammatory micro-environment caused by over-expression of α-syn and subsequently reduce the neurodegeneration associated with the chronic inflammation.
Specific Aims:
Aim 1: Determine whether the administration of ACP-196 can reduce the inflammatory micro-environment associated with α-syn.
Aim 2: Determine whether the administration of ACP-196 protects against α-syn induced neurodegeneration.
Aim1 (yr 2): Determine if the LRRK2G2019S mutation enhances the spread of pathogenic α-syn across interconnected neurons, consequently resulting in increased dopaminergic neuron death.
Aim 2 (yr 2): Determine if the absence of LRRK2 reduces the spread of α-syn across interconnected neurons and protects from α-syn inclusion-induced neuron death.
Potential Overlap: None.

Title: Validation of the Class II MHC Transactivator (CIITA) in Models of PD
Role: Co-Investigator
Time Commitment: 5%
Support Agency: Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Sonal Das
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 1/14/14 – 1/13/16
Annual Direct Costs: $100,000
Project Goals: The goal of this project is to determine whether blocking or down-regulating expression of CIITA is sufficient to attenuate the inflammatory process and neurodegeneration induced by α-syn in animal models.
Specific Aims:
Aim 1: Determine if knocking out CIITA expression in α-syn treated primary microglia attenuates MHCII expression and antigen processing.
Aim 2: Develop and test lenti-viral siRNA (lenti-siRNA) vectors to knockdown CIITA expression in primary microglial cultures treated with α-syn and IFNγ
Aim 3: Determine if lenti-siRNA knockdown of CIITA attenuates MHCII expression and antigen processing in primary microglia stimulated with α-syn and IFNγ.
Aim 4: Determine if siRNA knockdown of CIITA attenuates α-syn-induced neuroinflammation and neurodegeneration in vivo using an AAV2-SYN model of PD.
Potential Overlap: None.

Title: Role of MHC II proteins in Parkinson's-related inflammation
Role: Co-PI
Support Agency: RJG Foundation
Funding Agency Grants officer:
Anne B. Young
485 Madison Ave Fl 23
New York, NY 10022
Performance Period: 12/1/11 – 11/30/14
Annual Direct Costs: $100,000
Project Goals: The goal of this project is to determine whether a critical step in α-syn induced inflammation is microglial antigen presentation to T lymphocytes mediated by MHCII, leading to downstream induction of inflammatory mediators and neurodegeneration.
Specific Aims:

Aim 1: Using primary microglia cultures, determine whether alpha-synuclein internalization by microglia leads to MHCII translocation through an IgG and FcγR dependent process.
Aim 2: Using primary microglia and T lymphocyte co-cultures, determine whether internalized α-syn triggers MHCII dependent antigen presentation resulting in T cell proliferation and microglial activation
Aim 3: Using our in vivo AAV2-SYN mouse model, determine whether deletion of MHCII proteins attenuates synuclein-induced inflammation and neurodegeneration.
Potential Overlap: None.

Title: Role of HLA/MHCII in Parkinson's Disease Pathogenesis (R01NS092122)
Role: Co-Investigator
Support Agency: National Institutes of Health pass through Emory University
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 9/30/15 – 6/30/16
Annual Direct Costs: $32,132
Project Goals: The goal of this project is to investigate the molecular mechanisms underlying the association between a common genetic variant at rs3128892 in the HLA-DRA gene of the Major Histocompatibility Complex-II locus and increased risk for late-onset Parkinson's disease
Specific Aims:
The Standaert laboratory at UAB will recruit 160 patients with idiopathic PD as well as 160 age, and sex-matched healthy control subjects for genotype determination from a saliva sample followed by venipuncture for collection of peripheral blood for immunophenotyping and epigenetic analyses, and a clinical exam in accordance with NINDS guidelines for the Parkinson's Disease Biomarkers Database.
Potential Overlap: None.

Title: Evaluation of the effects of a novel nicotinic agonist, AZD1446, on neurochemical and electrophysiologic endpoints in DYT1 mouse models
Role: PI
Time Commitment: 1% calendar months
Support Agency: Dystonia Medical Research Foundation
Funding Agency Grants officer:
Jan K. Teller, MA, PhD
One East Wacker Dr, Ste 2810
Chicago, IL 60601
Performance Period: 5/1/15 – 10/31/16
Annual Direct Costs: $50,000
Project Goals: This project will use in vivo microanalysis to evaluate the effect of a novel nicotinic agonist, AZD1446, on striatal dopamine release in DYT1 knock-in animals.
Specific Aims:
Aim 1: In the Standaert lab, we will use in vivo microdialysis to evaluate the effect of a novel nicotinic agonist, AZD1446, on striatal dopamine release in DYT1 knock-in animals.
Aim 2: In the Pisani Lab, we will assess the effects of AZD1446 on striatal electrophysiology, particularly striatal plasticity as measured by LTD, LTP, and depotentiation.
Potential Overlap: None.

Title: The role of the JAK/STAT Pathway in the human of Parkinson's Disease
Role: Co-Investigator
Time Commitment: 5%

Support Agency: The Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Todd Sherer
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 2/13/17 – 2/12/18
Annual Direct Costs: $100,000
Project Goals: We will investigate the JAK/STAT pathway by studying immune cells obtained from individuals with PD and healthy controls. Our hypothesis is that monocytes and T-cells (immune system cells) from PD patients will exhibit heightened activation of the JAK/STAT pathway and gene expression compared to controls. This work will establish whether the JAK/STAT pathway is a valid therapeutic target.
Potential Overlap: None.

Title: Clinician-input Study: How the Fox Wearable Companion Mobile Application can Influence Treatment and Care (CIS-PD)
Role: Site PI
Time Commitment: 1%
Support Agency: The Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Todd Sherer
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 10/1/16 – 11/14/17
Annual Direct Costs: $46,640
Project Goals: The goal of this clinical trial is to assess feasibility and utility of the remote capture wearable device data from Parkinson's disease patients in clinical practice.
Potential Overlap: None.

Title: Innate and Adaptive Immunity in Parkinson Disease (P20NS092530)
Role: PD/PI
Time Commitment: 5%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 7/1/15 – 6/30/18
Annual Direct Costs: No cost extension
Project Goals: The goal of this project is to create the team, environment, and capability to explore innate and adaptive immunity in PD and lead to the development of a future Udall Center of Excellence focusing on neuroinflammation in PD.
Specific Aims:
Aim 1: Solidify the core collaborative team necessary for a future P50 Udall Center application.
Aim 2: Identify critical neuroimmunological endpoints and test key hypotheses in PD model systems that will provide the feasibility, significance, and impact needed for a successful future P50 application.
Aim 3: Develop the process and pipeline needed to study human subject populations, particularly in very early stages of clinical PD, and establish the operational basis for an effective Udall Center clinical core.
Potential Overlap: None.

Current/Pending/Previous Support

Ashley Harms

Current Support, continuing since the last reporting

Title: Mechanisms of alpha-synuclein mediated inflammation in multiple system atrophy (R01NS107316)
Role: PI
Time Commitment: 38%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 6/1/18 – 3/31/23
Annual Direct Costs: $218,750
Project Goals: The goal of this project is to investigate the contribution of brain-resident and peripheral immune cells in initiating and sustaining inflammation, and target these cells as a novel way of blocking disease progression.
Specific Aims:
Aim 1: Selective deletion of MHCII CNS from resident microglia is protective against α-syn-induced monocyte and T cell invasion, inflammation, demyelination, and neurodegeneration in a model of MSA.
Aim 2: Peripheral deletion of CCR2 and pharmacological blockade of CCR2 attenuate α-syn-induced demyelination, and neurodegeneration in a model of MSA.
Aim 3: Inhibition of T cell entry into the CNS attenuates α-syn-induced monocyte entry, demyelination, and neurodegeneration in a model of MSA.
Potential Overlap: None.

Title: Validation of CD4 T cell dependent neurotoxicity in an alpha-synuclein model of PD
Role: PI
Time Commitment: 15%
Support Agency: Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
To be determined
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 8/1/18 – 11/22/19 no cost extension
Annual Direct Costs: $90,909
Project Goals: The goal of these studies will be to examine the CD4 T cell infiltration in response to alpha-synuclein overexpression, and explore if genetic knockout of these cells curbs inflammation and neurodegeneration.
Specific Aims:
Aim 1: Determine the timing of α-syn-induced CD4 T cell infiltration.
Aim 2: Determine whether deletion of CD4 is sufficient to attenuate α-syn-induced inflammation via microglia activation and peripheral immune cell infiltration.
Aim 3: Determine whether deletion of CD4 is sufficient to attenuate α-syn-induced inflammation via neurodegeneration.
Potential Overlap: None.

Title: Validation of CCR2-Dependent Monocyte Entry in Alpha-Synuclein-Induced Toxicity (12087.01)
Role: PI
Time Commitment: 15%
Support Agency: Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Terina Martinez, PhD
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 6/1/18 – 12/9/19 no cost extension
Annual Direct Costs: $103,131
Project Goals: The goal of these studies will be, for the first time, to examine whether blocking CCR2+ monocyte entry via the small molecule inhibitor RO523444 attenuates α-syn-induced inflammation and neurodegeneration in the AAV2-SYN model of PD.
Specific Aims:
Aim 1: Determine whether the small molecule inhibitor RO5254444 blocks CCR2-dependent monocyte/macrophage entry and inflammation in an α-syn model of PD;
Aim 2: Determine whether use of this inhibitor is neuroprotective.
Potential Overlap: None.

Current Support, new since the last reporting

Title: Interactions of Gut Microbiome, Genetic Susceptibility and Environmental Factors in Parkinson's Disease (W81XWH1810509)
Role: Co-Investigator
Time Commitment: 17%
Support Agency: Department of Defense
Funding Agency Grants officer:
Jason Kuhns
Performance Period: 9/1/18 – 8/31/22
Annual Direct Costs: $103,195
Project Goals: The goal of this study is to identify the organisms in the gut that interact with genetic and environmental risk factors of PD. Microbiome can be easily altered; thus, successful completion of this project will provide feasible means to predict, prevent and treat PD.
Specific Aims:
Aim 5. Investigate the mechanisms of interactions. Hypothesis: Corynebacterium will increase alpha-synuclein and accelerate parkinsonian phenotypes in a mouse model. Rationale: Transplant of a PD microbiome has been shown to enhance parkinsonian phenotypes in alpha-synuclein over-expressing mice,24 but the responsible microorganims are unknown. Approach: We will use Thy1-SNCA specific pathogen free and germ-free mice and test the effect of introducing Corynebacterium on alpha-synuclein and relevant phenotypes.
Potential Overlap: None.

Title: Innate and Adaptive Immunity in Parkinson Disease: Project 1 - Role of Innate Immune Cells in Human Parkinson Disease (P50NS108675)
Role: Co-Investigator
Time Commitment: 5%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223

6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 9/30/18 – 7/31/23
Annual Direct Costs: $191,409
Project Goals: The goal of this project is to explore the overarching hypothesis that innate immune cells are activated towards a pro-inflammatory phenotype early in PD. We theorize that blocking this activation will protect from PD progression.
Specific Aims:
Aim 1: In the same population of 60 patients with de novo PD and 60 age- and sex-matched controls, determine whether there is change over time in monocytes populations assessed by flow cytometry or in blood cytokines and chemokines.
Aim 2: Determine the relationship between baseline measures of inflammation and longitudinal clinical outcomes, particularly cognition, in this population of early de novo PD subjects.
Potential Overlap: None.

Pending Support

None.

Previous Support, ended since the last reporting

Title: Advancing PINK1 KO Rat Animal Models of PD (11380.01)
Role: Collaborator
Time Commitment: 3%
Support Agency: Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Shalini Padmanabhan
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 11/1/17 – 4/30/19
Annual Direct Costs: $99,936
Project Goals: The goals of this project are to determine the mechanisms of neurodegeneration in PINK1 KO rats and to determine the extent to which neuroinflammation contributes to hind limb paresis onset or recovery.
Specific Aims:
Aim 1: Determine the mechanisms of neurodegeneration in PINK1 KO rats.
Aim 2: Determine the extent to which neuroinflammation contributes to hind limb paresis onset or recovery in PINK1 KO rats.
Potential Overlap: None.

Title: Targeting MHCII proteins on CNS resident microglia in an alpha-synuclein model of Parkinson disease (8561.01)
Role: PI
Time Commitment: 5%
Support Agency: Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Julia Keefe
Grand Central Station
PO Box 4777
New York, NY 10163-4777

Performance Period: 11/1/16 – 2/15/19
Annual Direct Costs: No cost extension
Project Goals: The goal of this project is to determine whether selective deletion of MHCII proteins on resident microglia is sufficient to attenuate α-syn-induced inflammation, peripheral immune cell infiltration, and neurodegeneration.
Specific Aims:
Aim 1: Determine if murine MHCII proteins can be selectively deleted from resident CX3CR1-expressing microglia in vivo and the efficiency of doing so.
Aim 2: Determine if selective deletion of MHCII proteins on CX3CR1-expressing microglia attenuates α-syn-induced inflammation and infiltration of peripheral immune cells.
Aim 3: Determine if selective deletion of MHCII proteins on CX3CR1-expressing microglia is protective against α-syn-induced neurodegeneration.
Potential Overlap: None.

Title: Mechanisms of LRRK2 Neurotoxicity (R01NS064934)
Role: Co-Investigator
Time Commitment: 5%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 4/1/16 – 3/31/21
Annual Direct Costs: $218,750
Project Goals: This project will investigate the cellular contributors to G2019S-LRRK2-mediated neurotoxicity in Parkinson's disease.
Specific Aims:
Aim 1: G2019S-LRRK2 expression in myeloid cells upregulates chemotaxis in response to neuronal α-synuclein inclusions to promote neurodegeneration.
Aim 2: LRRK2 knockout in myeloid cells downregulates chemotaxis in response to neuronal α-synuclein inclusions and protects from neurodegeneration.
Aim 3: LRRK2 scaffolds the assembly of actin filament networks in the leading edge of differentiated and mobile myeloid cells.
Potential Overlap: None.

Previous Support, no change since last reporting

Title: Validation of CCR2-dependent monocyte entry in alpha-synuclein-induced toxicity (12087)
Role: PI
Time Commitment: 20%
Support Agency: Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Adria Martig
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 9/1/16 – 8/31/17
Annual Direct Costs: $90,909

Project Goals: This project will test whether monocyte entry from the periphery is required for α-syn-induced inflammation and neurodegeneration, and that blocking CCR2-dependent monocyte infiltration into the CNS is neuroprotective from α-syn mediated neurodegeneration.
Specific Aims:
Aim 1: To characterize the timing and extent of monocyte entry into the brain in response to α-syn fibrils in mice
Aim 2: To determine whether blocking CCR2 protects against pathologic α-syn induced dopamine neuron death
Potential Overlap: None.

Title: BTK Inhibitors and Their Potential Role in Inhibiting the Pro-Inflammatory Microenvironment Associated with Neurodegeneration
Role: Co-Investigator
Time Commitment: 30%
Support Agency: Acerta Pharma B.V.
Funding Agency Grants officer:
Cecile Krejsa, PhD
15400 SE 30th Place Suite 206,
Bellevue, WA 98007
Performance Period: 1/1/15 – 12/5/16
Annual Direct Costs: $100,679
Project Goals: The goal of this project is to evaluate whether the administration of ACP-196 can reduce the pro-inflammatory micro-environment caused by over-expression of α-syn and subsequently reduce the neurodegeneration associated with the chronic inflammation.
Specific Aims:
Aim 1: Determine whether the administration of ACP-196 can reduce the inflammatory micro-environment associated with α-syn.
Aim 2: Determine whether the administration of ACP-196 protects against α-syn induced neurodegeneration.
Aim1 (yr 2): Determine if the LRRK2G2019S mutation enhances the spread of pathogenic α-syn across interconnected neurons, consequently resulting in increased dopaminergic neuron death.
Aim 2 (yr 2): Determine if the absence of LRRK2 reduces the spread of α-syn across interconnected neurons and protects from α-syn inclusion-induced neuron death.
Potential Overlap: None.

Title: Validation of the Class II MHC Transactivator (CIITA) in Models of PD (8561)
Role: Co-Investigator
Time Commitment: 25%
Support Agency: Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Sonal Das
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 1/14/14 – 1/13/16
Annual Direct Costs: $100,000
Project Goals: The goal of this project is to determine whether blocking or down-regulating expression of CIITA is sufficient to attenuate the inflammatory process and neurodegeneration induced by α-syn in animal models.
Specific Aims:
Aim 1: Determine if knocking out CIITA expression in α-syn treated primary microglia attenuates MHCII expression and antigen processing.
Aim 2: Develop and test lenti-viral siRNA (lenti-siRNA) vectors to knockdown CIITA expression in primary microglial cultures treated with α-syn and IFNγ

Aim 3: Determine if lenti-siRNA knockdown of CIITA attenuates MHCII expression and antigen processing in primary microglia stimulated with α-syn and IFNγ.
Aim 4: Determine if siRNA knockdown of CIITA attenuates α-syn-induced neuroinflammation and neurodegeneration in vivo using an AAV2-SYN model of PD.
Potential Overlap: None.

Title: Role of MHC II proteins in Parkinson's-related inflammation
Role: Co-PI
Time Commitment: 25%
Support Agency: RJG Foundation
Funding Agency Grants officer:
Anne B. Young
485 Madison Ave Fl 23
New York, NY 10022
Performance Period: 12/1/11 – 11/30/14
Annual Direct Costs: $100,000
Project Goals: The goal of this project is to determine whether a critical step in α-syn induced inflammation is microglial antigen presentation to T lymphocytes mediated by MHCII, leading to downstream induction of inflammatory mediators and neurodegeneration.
Specific Aims:
Aim 1: Using primary microglia cultures, determine whether alpha-synuclein internalization by microglia leads to MHCII translocation through an IgG and FcγR dependent process.
Aim 2: Using primary microglia and T lymphocyte co-cultures, determine whether internalized α-syn triggers MHCII dependent antigen presentation resulting in T cell proliferation and microglial activation
Aim 3: Using our in vivo AAV2-SYN mouse model, determine whether deletion of MHCII proteins attenuates synuclein-induced inflammation and neurodegeneration.
Potential Overlap: None.

Title: Innate and Adaptive Immunity in Parkinson Disease; Project 1: PD-linked Susceptibilities in Myeloid Cell CNS Infiltration (P20NS092530)
Role: Co-Investigator
Time Commitment: 30%
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Beth-Anne Sieber
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 7/1/15 – 6/30/18 (Dr. Harms support/effort ended 9/30/17)
Annual Direct Costs: No cost extension
Project Goals: The goal of this project is to determine whether G2019S-LRRK2 increase α-syn-induced peripheral myeloid cell entry into the CNS, and whether LRRK2 inhibition blocks this process.
Specific Aims:
Aim 1: G2019S-LRRK2 expression promotes an exaggerated peripheral response of myeloid cell infiltration and pro-inflammatory responses.
Aim 2: LRRK2-knockout mice, or treatment of WT-rodents with orally available LRRK2 kinase inhibitors, will block myeloid cell infiltration and pro-inflammatory responses in the CNS.
Potential Overlap: None.

Interactions of gut microbiome, genetic susceptibility and environmental factors in Parkinson's disease

PD170080P1

W81XWH1810509

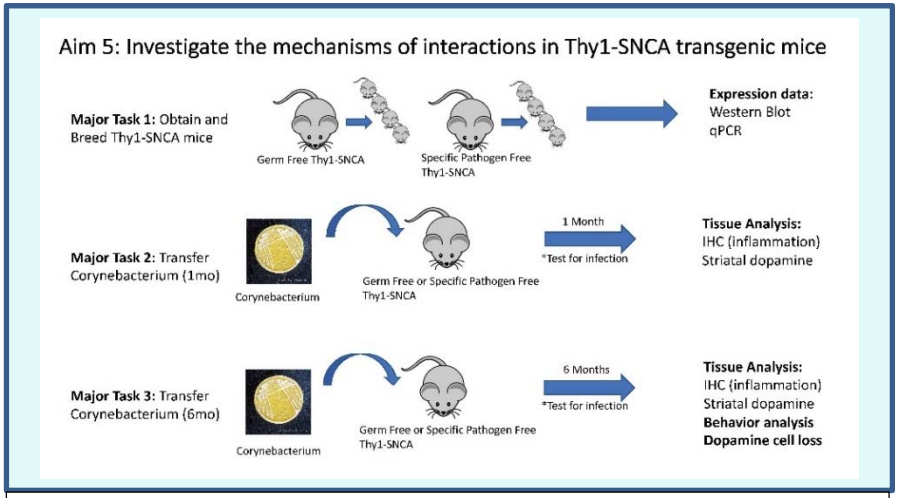
PI: David Standaert, MD, PhD **Org:** University of Alabama at Birmingham **Award Amount:** $635,001

Study/Product Aim(s)

- This is a component of a Partnering PI award
- The overall objective of the collaboration is to identify microbial pathways that contribute to the cause of Parkinson disease (PD), and study the interaction of microbial factors with host genes
- The role of this project is to examine the effect of specific organisms identified from the microbiome of humans in a rodent model of PD
- We aim to determine the effect of Corynebacterium on the mouse Thy1-alpha Syn model of PD

Approach

In this project, we will use a previously created mouse model of PD with transgenic expression of human alpha-synuclein. After establishing a colony of these animals, we will transfer them to the UAB Gnotobiotic Core Facility where they will be maintained germ free. We will then repopulate them with Corynebacterium and examine histological, biochemical and behavioral outcomes.



We have obtained the Thy1-SYN transgenic mice and have begun breeding them in specific pathogen free conditions. Thus far we have bred 2 generations of mice and have verified the genotype by establishing a genotyping protocol.

Timeline and Cost

Activities / CY	18	19	20	21	22
Re-deriving Thy1-SNCA mouse in gnotobiotic facility and breeding of SPF mice)					
Transfer of Corynebacterium to SPF & GF mice for 1 month time pt					
Transfer of Corynebacterium to SPF & GF mice for 6 month time pt					
Estimated Budget ($K)	**$51**	**$151**	**$158**	**$171**	**$104**

Updated: 9/30/19

Goals/Milestones

CY18 Goal – Initial animal husbandry and validation

☑ Obtain, breed, and genotype required mouse strain

CY18 Goals – Model validation, transfer to gnotobiotic core facility

☑ ReValidate mouse model by genetic and western blot analysis

☐ derive mouse strain under gnotobiotic conditions

CY19 Goal – Short term studies in gnotobiotic mice

☐ Establish stable colony of gnotobiotic animals

☐ Infect gnotobiotic animals with Corynebacterium

CY20 Goal – One month studies

☐ Collection of tissues for one month endpoint

☐ Immunohistochemical and neurochemical analysis

CY21/22 Goals

☐ Infect gnotobiotic animals with Corynebacterium

☐ Collection of tissues for six month endpoint

☐ Immunohistochemical and neurochemical analysis

☐ Data analysis and manuscript preparation

Budget Expenditure to Date (9/1/18 – 8/31/19)

Projected Expenditure: $153,245

Actual Expenditure: $143,977