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TITLE: Reducing tau as a Therapeutic Strategy for Improving Cognitive Dysfunction in Parkinson's Disease

PRINCIPAL INVESTIGATOR: Laura Volpicelli-Daley, PhD

RECIPIENT: University of Alabama at Birmingham
Birmingham, AL 35294

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6. AUTHOR(S)

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University of Alabama at Birmingham
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Birmingham, AL 35294-0001

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14. ABSTRACT

The goal of this proposal is to address the NETPR mission by assessing tau reduction as a therapeutic intervention point for preventing dementia and mood disorders in PD. Neuronal protein inclusions composed of α-synuclein (α-syn) called Lewy bodies and Lewy neurites are primary characteristics in brains from PD patients. To test this, we are using a model of PD in which exposure of neurons to α-syn fibrils induces formation of inclusions from endogenously expressed α-syn that recapitulate many features of inclusions in diseased brains. During this research period we found that there are fewer α-syn inclusions in cultured neurons from tau knockout mice compared to control neurons. In the next cycle we will determine if reduction of tau prevents inclusion formation in the cortex, hippocampus and amygdala, *in vivo*.

15. SUBJECT TERMS

Parkinson's disease, Lewy body dementias, α-synuclein, tau, cognition, Lewy body, axonal transport, anxiety, depression

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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TABLE OF CONTENTS

1. INTRODUCTION. The goal of this proposal is to address the NETPR mission by assessing tau reduction as a therapeutic intervention point for preventing nonmotor manifestations of Parkinson's disease, PD, specifically dementia and mood disorders. Neuronal protein inclusions composed of α-synuclein (α-syn) called Lewy bodies and Lewy neurites are primary characteristics in brains from Parkinson's disease patients. Our hypotheses are **that reduction of tau will** 1) **slow the spread of pathologic α-syn, and 2) prevent neuronal dysfunction and behavioral defects related to cognition and mood disorders that caused by these inclusions.** To test this, we will use a model of PD in which exposure of neurons to α-syn fibrils induces formation of inclusions from endogenously expressed α-syn that recapitulate many features of inclusions in diseased brains. For all experiments we will use tau +/+, tau +/- and tau -/- mice. Our first goal is to use primary hippocampal neurons to determine if absence of tau reduces formation of α-syn inclusions. We also will determine if reduction of tau rescues defects in axonal transport caused by formation of a-syn inclusions. Our second goal is to determine if reducing tau prevents formation and propagation of α-syn inclusions throughout the brain. We will inject α-syn fibrils into the mouse striatum. We will perform behavioral tests of cognition, depression and anxiety. We will then perform immunohistochemistry for α-syn phosphorylated at Serine 129, a marker of inclusion formation. The abundance of inclusions in the amygdala, striatum and cortex, brain regions critical for cognition, will be quantified.

2. KEYWORDS: Parkinson's disease, Lewy body dementias, α-synuclein, tau, cognition, Lewy body, axonal transport, anxiety, depression

3. ACCOMPLISHMENTS:

a. Major goals of project and accomplishments to date:

Specific Aim 1: Test the hypothesis that absence of tau prevents α-synuclein inclusion formation

Major Task 1: Determine if tau ablation inhibits overall abundance of α-syn inclusions produced by fibrils in primary hippocampal neuron. Months 1-12

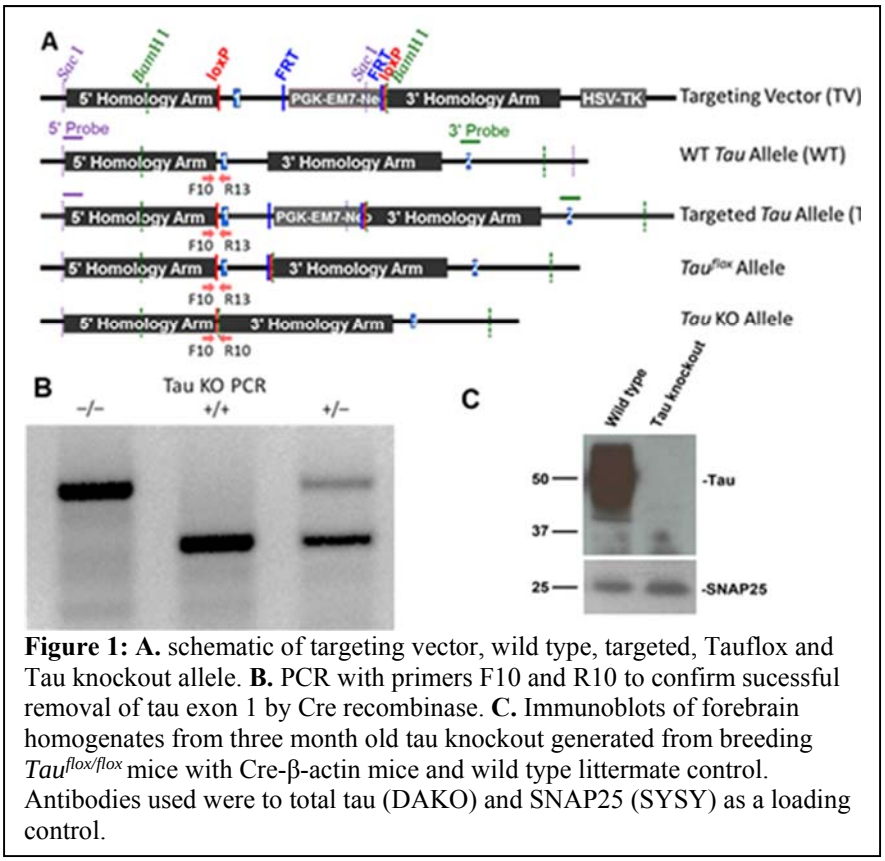


Figure 1: A. schematic of targeting vector, wild type, targeted, Tauflox and Tau knockout allele. **B.** PCR with primers F10 and R10 to confirm sucessful removal of tau exon 1 by Cre recombinase. **C.** Immunoblots of forebrain homogenates from three month old tau knockout generated from breeding $Tau^{flox/flox}$ mice with Cre-β-actin mice and wild type littermate control. Antibodies used were to total tau (DAKO) and SNAP25 (SYSY) as a loading control.

a. We obtained constitutive tau knockout mice for our collaborator. These mice were generated by crossing $Tau^{flox/flox}$ to mice expressing β-actin Cre. By using these mice, in the future we could utilize the mice to generate Tamoxifen-inducible tau knockout mice to ablate tau after initiation of a-syn inclusions.

Both our collaborator and our lab had problems with genotyping. In particular, we found nonspecific PCR bands in the genotyping PCR from the tau +/+ mice that caused us to mistakenly identify our wildtype mice as heterozygotes. We therefore designed new genotyping primers and performed extensive troubleshooting of our PCR conditions. We now have a working genotyping protocol that reliably identifies wild type, knockout and heterozygous mice. However, this problem delayed our breeding and generation of cohots of tau +/+ and tau -/- mice.

We are now reliably breeding tau +/- mice and are generating tau +/+ and tau -/- mice for experiments.

b. We generated α-syn monomer. We have 15 mg of protein which is enough to complete the study. The protein was subjected to the Pierce LAL endotoxin clean up kit and our endotoxin units are approximately 0.01 ng/mL protein. We found that freezing our fibrils in the -80 causes disaggregation. We therefore prepare our fibrils fresh for each experiment. The fibrils are characterized by sedimentation assays in which the fibrils are spun at 100,000xg and the supernatant and pellet are resolved by SDS-PAGE if >50% of a-syn is found in the pellet, we reliably can seed a-syn inclusion formation in the primary neurons.

c. In a study performed with collaborators, we found that 200 ng/mL of fibrils is sufficient to produce abundant a-syn inclusions in primary neurons (Abdelmotilib et al., 2017). We are therefore using this concentration in our primary neuron experiments.

d. We have added fibrils to primary hippocampal neurons from tau +/+ and tau -/- mice. Neurons were fixed and immunofluorescence using an antibody to p-a-syn was performed and the abundance of inclusions was quantified. At 7 days after adding fibrils there was no difference in the abundance of inclusions between tau +/+ and tau -/- mice. At fourteen days after adding fibrils there was a significant reduction in the abundance of inclusions in tau -/- mice compared to tau +/+ mice.

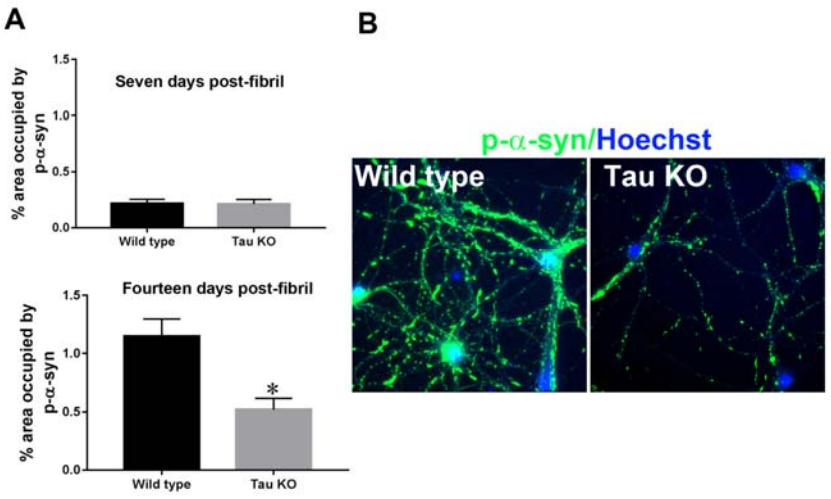


Figure 2: A. Primary hippocampal neurons from wild type or tau KO mice were exposed to fibrils and fixed 7 or 14 days layer. Immunofluorescence was performed for p-α-syn as a marker of inclusion formation. Confocal images were captured and the abundance of α-syn inclusions as the percentage area of the field occupied by p-α-syn. At 14 days after fibril exposure, absence of tau significantly reduces the abundance of inclusions (N=20 fields quantified from 2 independent experiments). **B.** Representative confocal image of p-α-syn inclusions in wild type and tau knockout neurons.

Major Task 2: Determine if tau ablation prevent spread of α-syn inclusions from axons to soma.

We have quantified the % soma that have inclusions. There appears to be more inclusions in the soma of tau -/- mice than tau +/+ mice. We plan to repeat these experiments. One of our hypotheses is that reducing tau

prevents alpha-synuclein from being transported to the presynaptic terminal and consequently, more remains in the soma. Thus, more total levels of a-syn in the soma results in more somal inclusions. This may prevent the propagation of a-syn to neighboring neurons. We will use microfluidic chambers to further test this hypothesis.

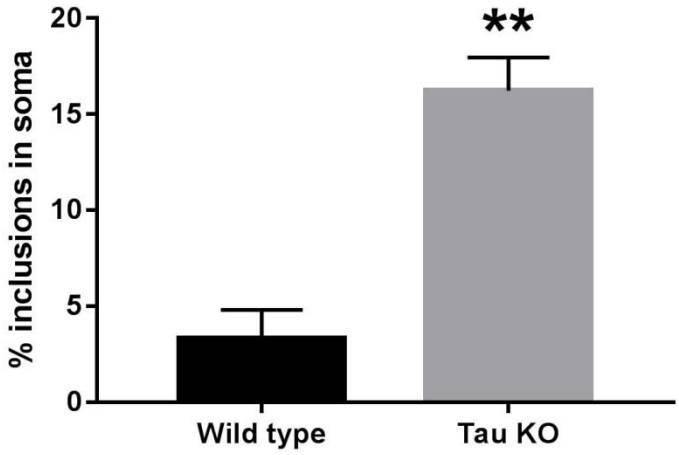
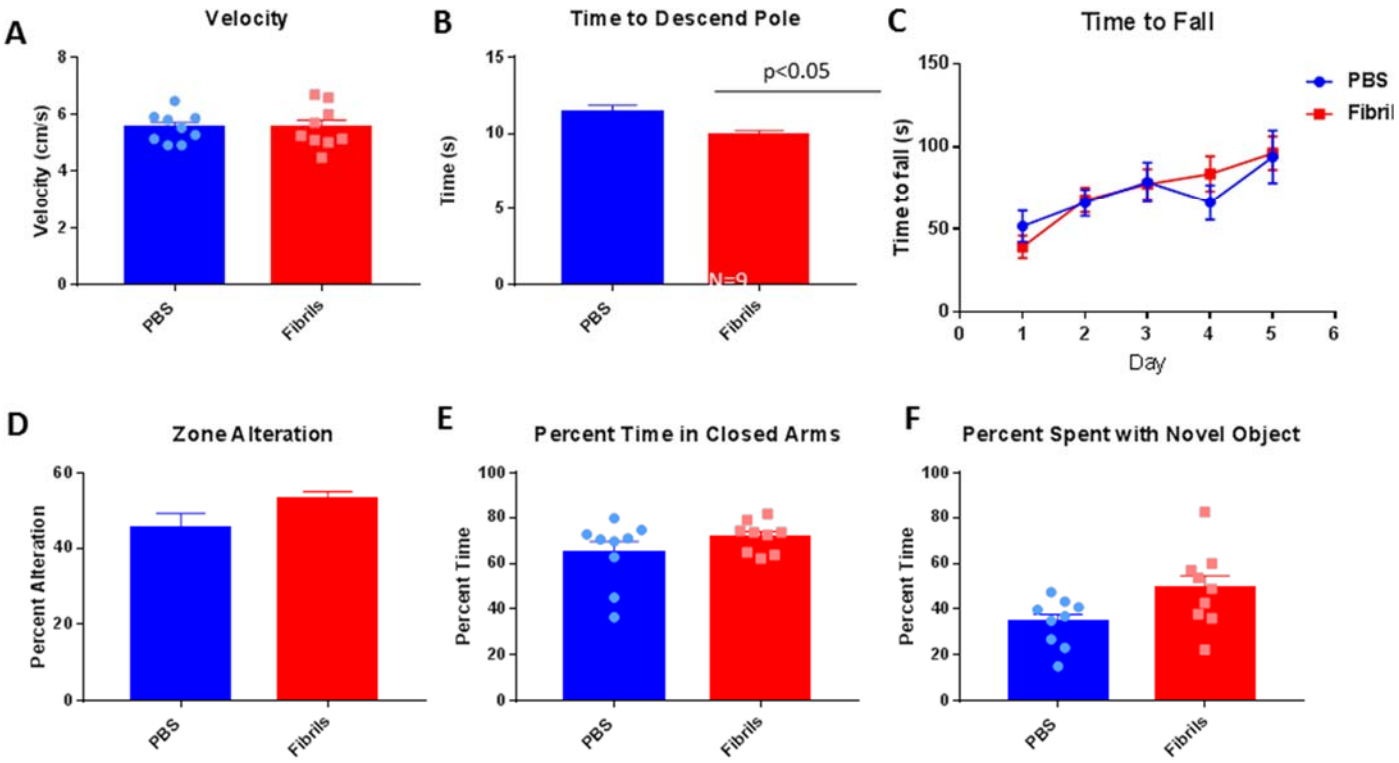


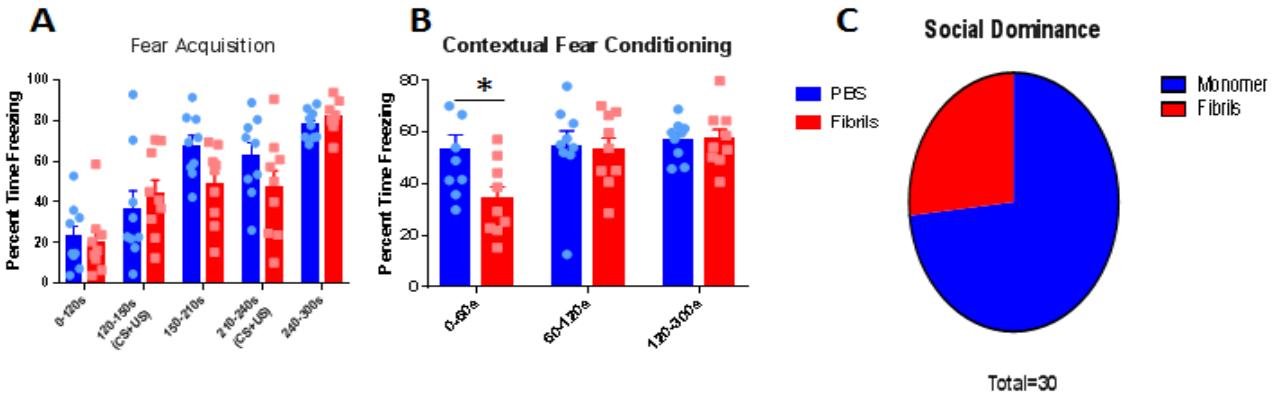
Figure 3: A. Primary hippocampal neurons from wild type or tau KO mice were exposed to fibrils and fixed 14 days layer. Immunofluorescence was performed for p-α-syn as a marker of inclusions and NeuN to identify neuronal soma. Data is presented as the neurons with inclusions in soma as percentage of total neurons. (N=20 fields quantified from 2 independent experiments).

Major Task 3: Does tau ablation restore axonal transport of TrkB-GFP and GFP-LC3?
We have performed the experiments for axonal transport of TrkB-GFP and are in the process of analyzing the data.

Specific Aim 2: Determine if tau ablation prevents the formation of α-syn inclusions locally or in downstream brain regions and prevents behavioral defects produced by these inclusions.
Major Task 1: Breed tau +/+ mice and tau -/- mice to generate 180-200 mice for this aim
We have bred tau +/- mice and obtained enough mice to inject 10 tau +/+, 10 tau +/- and 10 tau -/- with monomer and 10 tau +/+, 10 tau +/- and 10 tau -/- with fibrils.
Major Task 2: Inject 3 month old tau +/+ and tau -/- mice bilaterally with α-syn fibrils, monomeric α-syn or PBS
We have injected all the mice.
Major Task 3: Behavioral experiments
We performed a preliminary analysis of behavior using WT mice bilaterally injected with PBS or fibrils. The analyses were performed 5 months later. We performed the following behavioral tests: open field, rotarod, wire hang, pole test, elevated zero maze, novel object recognition, Y maze, fear conditioning, and the tube test as a test of prefrontal cortical function. As seen in figure 4, there were no significant differences between PBS and fibril injected mice in the following tests: open field (4A), pole test (4B), rotarod(4C), Y maze (4D), elevated zero maze (4E), or percent time with novel object (4F).

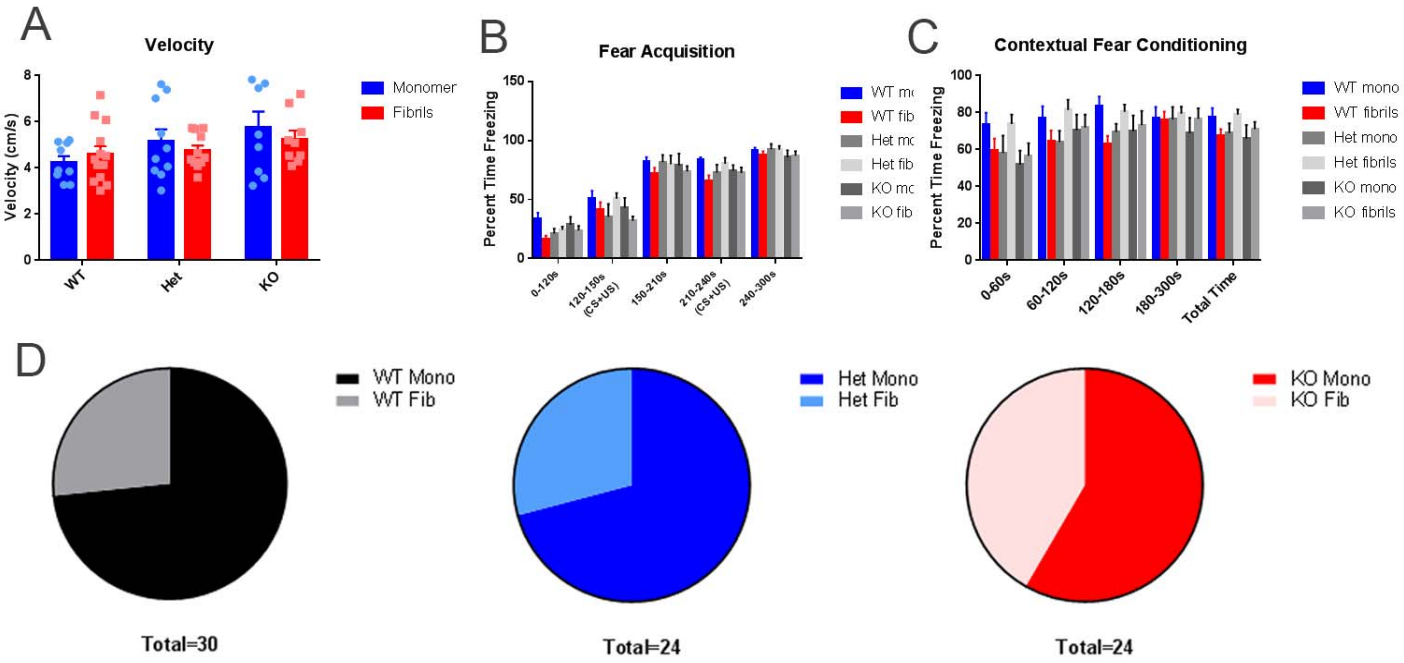


However, as shown in Figure 5, fibril injected mice did not have deficits in acquisition of fear learning (5B), but had impaired fear memory (5B). They also had decreased social dominance (5C) compared to controls.



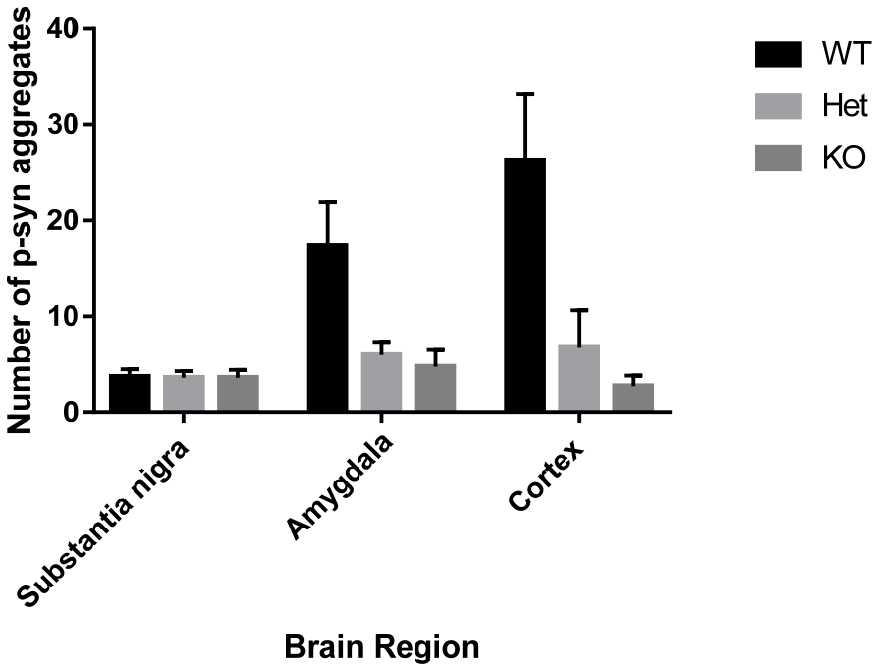
Based on the results of our preliminary cohort, we decided to perform the following behavior tests in the tau +/+, tau +/-, and tau -/- mice: open field (6A), fear conditioning (6B and 6C), and social dominance (6D). As expected, no mice showed deficits in the open field test. Additionally, no groups showed significant differences in fear acquisition. However, the WT fibril injected mice trended toward a lower percent time freezing at all time points, reaching significance at the third minute. This supports the findings from our preliminary cohort. However, the tau reduced groups (+/- and -/-) did not significantly differ from the +/+ control animals regardless of injection, suggesting tau reduction successfully ameliorated the deficits. In the social dominance test, fibril-injected animals were less dominant than their genotype-similar controls in both +/+ and +/- animals.

However, the tau -/- fibril-injected animals were not significantly different than monomer-injected controls, suggesting tau ablation rescued the effect.



Major Task 4: Perfuse mice, perform immunohistochemistry, and quantify inclusion abundance using unbiased stereology

We have performed the perfusions and immunohistochemistry of tau +/+, +/-, and -/- injected with monomer and fibrils. We have quantified inclusion abundance (Figure 7) in the substantia nigra, amygdala, and cortex of fibril-injected tau +/+, +/-, and -/- (monomer-injected controls did not have any inclusions). Excitingly, tau reduction decreased inclusion abundance in the amygdala and cortex.


Number of p-syn aggregates
40
30
20
10
0
WT
Het
KO
Substantia nigra
Amygdala
Cortex
Brain Region

b. What opportunities for training and professional development has the project provided?
Through our collaboration with Dr. Erik Roberson, our lab has learned more about how to perform and analyze behavioral tests, particularly those related to cognitive function.

c. How were results disseminated to communities of interest?
I would prefer to have the project closer to completion and ready to publish before presenting the data.

d. What do you plan to do the next reporting period to accomplish the goals?
We will complete the axonal transport studies. We will inject one more cohort of mice (tau +/+, tau +/-, tau -/-) and analyze behavior and p-synuclein inclusion formation at 3 months after fibril injections. We will then begin preparing the manuscript for publication.

4. **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:

My MD/PhD student, Lindsay Stoyka, was awarded a competitive NIH F30 fellowship based on data from this project. This will contribute to her future success as a physician scientist.

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

What was the impact on other disciplines?

What was the impact on technology transfer?

What was the impact on society beyond science and technology?

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:
Actual or anticipated problems or delays and actions or plans to resolve them
Changes that had a significant impact on expenditures
Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."
Publications, conference papers, and presentations
Journal publications.
Books or other non-periodical, one-time publications.
Other publications, conference papers and presentations.
Website(s) or other Internet site(s)

Nothing to report

7. Participants and other participating organizations

What individuals have worked on the project?

Laura Volpicelli-Daley, Principal Investigator. No change
Erik Roberson, Co- investigator, no change
Thomas van Groen, No change

Changes to personnel:

Name	Jessica Froula
Project role:	Research Assistant
Nearest person month worked	6
Contribution to project	Maintained mouse colonies, injected mice,
	Performed perfusions
Reason for leaving	Last Day 6/1/18; went to Graduate School

Name	Drake Thrasher
Project role:	Research Assistant
Nearest person month worked	6
Contribution to project	Maintains mouse colonies, injected mice,
	Performs perfusions, behavior tests
Reason for hiring	Took over from Jessica

Has there been a change in the active other suppor of the PI or key personnel?

Laura Volpicelli-Daley went from 36% effort to 34% effort. This is because she was awarded an R01 grant and had to change her effort somewhat so that it did not go above 100%

Please see updated Other Support for key personnel starting on the following page, with changes highlighted.

What other organizations have been involved?

Nothing to report

Active Support

Laura Volpicelli-Daley

Current Support

Title: Reducing Tau as a Therapeutic Strategy for Improving Cognitive Dysfunction in Parkinson's Disease (W81XWH-16-1 -0677)
Role: Principal Investigator
Time Commitment: 4.2 calendar months
Support Agency: Department of Defense
Funding Agency Grants officer:
Karen L. Petrore
US Army Medical Research Acquisition Activity Assistance Branch – Building 843
820 Chandler St
Ft. Detrick, MD 21702
Performance Period: 9/15/16 – 3/14/19
Annual Direct Costs: $124,994
Project Goals: The major goals are to test the following hypotheses: The absence of tau will 1) slow the spread of pathologic α-syn, and 2) prevent neuronal dysfunction and behavioral defects related to cognition and mood disorders that caused by these inclusions.
Specific Aims:
Aim 1: Determine if tau ablation inhibits spread of α-syn inclusions within the neuron and restores axonal transport defects produced by α-syn inclusions.
Aim 2: Determine if constitutive Tau knockout prevents the formation of α-syn inclusions either locally or in downstream brain regions and prevents behavioral defects produced by these inclusions.
Potential Overlap: None.

New active support since last reporting
Title: The impact of GBA mutations and glucosylceramide (GlcCer) synthase inhibition in in vitro and in vivo models of synucleinopathy
Role: PI
Time Commitment: 0.6 calendar months
Support Agency: Merck Sharp & Dohme Corp.
Funding Agency Grants officer:
J. Gregory Seedor
WP53B-330
770 Sumneytown Pike
West Point, PA 19486
Performance Period: 10/1/17 – 9/31/19
Annual Direct Costs: $67,340
Project Goals: The goal of this project is to characterize the impact of GBA mutations and glucosylceramide (GlcCer) synthase inhibition in in vitro and in vivo models of synucleinopathy
Specific Aims:
Aim 1: To characterize the effects of the GlcCer synthase inhibitor Ibiglustat on α-synuclein inclusions in primary mouse neuronal cultures
Aim 2: Test the hypothesis that heterozygosity for the L444P GBA mutation increases formation of α-synuclein inclusions in the cortex, hippocampus and amygdala of mice
Aim 3: Does heterozygosity for the L444P GBA mutation exacerbate development of α-synuclein inclusion-induced behavioral defects
Aim 4: Does oral administration of the GlcCer synthase inhibitor Ibiglustat reduce formation of α-synuclein inclusions in the cortex, hippocampus and amygdala of GBA+/+ or GBA+/L444P mice

Aim 5: Does oral administration of the GlcCer synthase inhibitor Ibiglustat reduce development of α-synuclein inclusion-induced behavioral defects in GBA+/+ or GBA+/L444P mice
Potential Overlap: None.

New active support since last reporting
Title: Role of presynaptic targeting of alpha-synuclein in the pathogenesis of Parkinson's Disease and Dementia with Lewy Bodies (R01NS102257)
Role: Principal Investigator
Time Commitment: 3.6 calendar months
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Margaret Sutherland
NIH/NINDS
Neuroscience Center, Room 2222
6001 Executive Blvd MSC 9525
Bethesda, MD 20892-9525
Performance Period: 5/1/18 – 2/28/23
Annual Direct Costs: $250,000
Project Goals: The goal of this project is to determine the role of LRRK2 substrates on alpha-synuclein targeting to the presynaptic terminal and its propensity to form pathologic inclusions.
Specific Aims:
Aim 1: Test the hypothesis that Rab10 enhances the presynaptic targeting of α-syn and reduces inclusion formation.
Aim 2: Test the hypothesis that Myosin Va and Myosin Vb target α-syn to the presynaptic terminal and reduce inclusion formation.
Aim 3: Test the hypothesis that LRRK2 kinase activity reduces presynaptic targeting of α-syn.
Potential Overlap: None.

New active support since last reporting
Title: Expansion Microscopy to Visualize Intracellular aSyn Pathology (12708.01)
Role: PI
Time Commitment: 0.6 calendar months
Support Agency: Michael J. Fox Foundation for Parkinson’s Research
Funding Agency Grants officer:
Nicole Polinski
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 2/2/18 – 2/1/19
Annual Direct Costs: $30,000
Project Goals: We will develop a novel imaging technique called expansion microscopy which will resolve localization of α-synuclein inclusions in the brain. The goals are: 1) Test the hypothesis that α-synuclein inclusions begin forming at the presynaptic terminal and over time, appear in the soma where they associate with autophagic/degradation machinery. 2) Perform expansion microscopy to resolve the subcellular localization α-synuclein inclusions and intracellular organelles at high (nanometer) resolution.
Specific Aims:
Aim 1: Test the hypothesis that α-synuclein inclusions begin forming at the presynaptic terminal and over time, appear in the soma where they associate with autophagic/degradation machinery.
Aim 2: Perform expansion microscopy to resolve the subcellular localization α-synuclein inclusions and intracellular organelles at high (nanometer) resolution.
Potential Overlap: None.

New active support since last reporting
Title: Innate and Adaptive Immunity in Parkinson Disease; Core C: Animal Models Core (P50NS108675)
Role: Core Leader
Time Commitment: 1.2 calendar months
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: $173,250
Project Goals: The overall goal of this core is to standardize the fibril model of PD to achieve consistent results across projects.
Specific Aims:
Aim 1: Produce low endotoxin recombinant α-syn.
Aim 2: Produce α-syn fibrils verified by quality control assays.
Aim 3: Inject sonicated fibrils into rat brains using personnel with extensive training and skills in stereotaxic surgery.
Aim 4: Obtain high quality fixed brain tissue sections and perform optimized immunohistochemistry and immunofluorescence to analyze abundance of pathologic α-syn throughout the brain and neuron death in the substantia nigra pars compacta.
Aim 5: Perform unbiased stereology so that neuron counts and quantitation of α-syn inclusions are consistent and reproducible across studies.
Potential Overlap: None.

New active support since last reporting
Title: Antisense oligonucleotide knockdown of the transcriptional repressor RIP140 to promote survival of dopaminergic neurons in a mouse model of PD (13436)
Role: Co-Investigator
Time Commitment: 0.36 calendar months
Support Agency: Michael J. Fox Foundation for Parkinson's Research pass through Southern Research
Performance Period: 12/1/17 – 11/30/18
Annual Direct Costs: $6,040
Project Goals: The goals of this application are to determine whether knockdown of the transcriptional repressor RIP140 can protect neurons from dysfunction and loss in the alpha-synuclein fibril model of Parkinson's Disease-associated pathology.
Potential Overlap: None.

New active support since last reporting
Title: Lysosomal enhancement strategies in dopaminergic neurodegeneration (R21NS101672)
Role: Collaborator
Time Commitment: 0.96 calendar months
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Margaret Sutherland
NIH/NINDS
Neuroscience Center, Room 2222
6001 Executive Blvd MSC 9525
Bethesda, MD 20892-9525
Performance Period: 9/30/17 – 8/31/19

Annual Direct Costs: $150,000
Project Goals: The major goal of this project is to study the impact of dopaminergic neuron specific overexpression of cathepsin D or dopaminergic neuron specific knockout of ZKSCAN3 on α-synuclein fibril-induced dopaminergic neurodegeneration.
Potential Overlap: None.

New active project, since last reporting; ***active support for Dr. Volpicelli-Daley begins 7/1/20***
Title: The Nigral Molecular Clock and Vulnerability to Neurodegeneration (R01NS108713)
Role: Co-Investigator
Time Commitment: 0.6 calendar months, yrs 3-5 only
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Margaret Sutherland
NIH/NINDS
Neuroscience Center, Room 2222
6001 Executive Blvd MSC 9525
Bethesda, MD 20892-9525
Performance Period: 7/1/18 – 6/30/23
Annual Direct Costs: $512,395
Project Goals: The goal of this proposal is to investigate the functional role of the molecular circadian clock in dopaminergic neurons of the substantia nigra and contributions to cell dysfunction and death in animal models of Parkinson Disease.
Potential Overlap: None.

Support ended since last reporting

Title: Innate and Adaptive Immunity in Parkinson Disease; Project 1: PD-linked Susceptibilities in Myeloid Cell CNS Infiltration (P20NS092530)
Role: Co-Investigator
Time Commitment: 0.6 calendar months
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, no cost extension
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.

Title: Identification of Robust and Relevant Pre-Clinical Phenotypes for LRRK2 Therapeutics
Role: Co-PI
Time Commitment: 1.2 calendar months, effort decreased from 6.0 calendar months
Support Agency: Michael J. Fox Foundation for Parkinson's Research

Funding Agency Grants officer:
Marco Baptista
Grand Central Station
PO Box 4777
New York, NY 10163-4777
Performance Period: 2/27/15 – 2/26/18
Annual Direct Costs: $197,031
Project Goals: The goal of this project is to identify disease-relevant endpoints that show greatest dependency on LRRK2 kinase activity so that these assays may be prioritized and standardized in LRRK2 therapeutic pipelines.
Specific Aims:
Aim 1: The first goal is to test whether LRRK2 inhibition blocks α -synuclein inclusions and related toxicities in dissociated neurons.
Aim 2: The second goal is to determine whether LRRK2 inhibition ameliorates deficits in dopamine transmission caused by α -synuclein inclusions in the SNpc.
Aim 3: The third goal assesses the impact of LRRK2 inhibition on transmission of α -synuclein inclusions among interconnected neurons.
Aim 4: The fourth goal is to discover whether LRRK2 inhibition blocks dopaminergic neurodegeneration and TH-fiber loss in rats, and associated neuroinflammation, induced by α-synuclein inclusions in the SNpc.
Potential Overlap: None.

Title: Mechanisms of LRRK2 Neurotoxicity (R01NS064934)
Role: Co-Investigator
Time Commitment: 0.96 calendar months
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.

Title: Defining α-synuclein conformers responsible for PD phenotypes in mice (12708)
Role: PI
Time Commitment: 1.2 calendar months
Support Agency: Michael J. Fox Foundation for Parkinson's Research
Funding Agency Grants officer:
Nicole Polinski
Grand Central Station
PO Box 4777

New York, NY 10163-4777
Performance Period: 5/1/16 – 8/30/18, no cost extension
Annual Direct Costs: No cost extension
Project Goals: Defining α-synuclein conformers responsible for PD phenotypes in mice
The goal of this project is to meticulously define and isolate reproducible conformers of α-syn and determine which species produce neuropathological and neurodegenerative outcomes in mice. Through our work, we will develop SOPs for producing defined conformers that can be standardized in pre-clinical PD models for reliable phenotypes.
Specific Aims:
Aim 1: Develop SOPs for producing defined conformers that can be standardized in pre-clinical PD models for reliable phenotypes
Aim 2: Determine whether alpha-synuclein oligomers or short fibrils are responsible for PD-related phenotypes
Potential Overlap: None.

Title: Efficacies and Pharmacodynamic Assays for LRRK2 Small-Molecule Inhibitors (R21NS097643)
Role: Co-Investigator
Time Commitment: 0.96 calendar months
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Mary Ann Pelleymounter, PhD
Neuroscience Center, Room 2117
6001 Executive Blvd MSC
Bethesda, MD 20892
Performance Period: 9/1/16 – 8/31/17 (no cost extension request in progress to 12/31/17)
Annual Direct Costs: $250,000
Project Goals: The major goals are to 1) determine whether LRRK2 kinase inhibitors can block neurotoxicities and inflammation associated with α-synuclein after the onset of neurodegeneration and 2) determine the minimum level of LRRK2 kinase inhibition required for neuroprotective benefit.
Specific Aims:
Aim 1: To establish profiles for WT and G2019S-LRRK2 kinase inhibition by PF-475 and PF-360 in mouse brain, and the relationship to phospho-LRRK2 protein in exosomes.
Aim 2: To identify EDs for LRRK2 kinase inhibitors in neuroprotection and anti-neuroinflammation activities in mouse models of PD.
Aim 3: To determine LRRK2 inhibitor efficacies pre- vs. post-disease initiation.
Potential Overlap: None.

Title: Alpha-Galactosidase A- a Novel Target for Reducing Alpha-synuclein Toxicity (R21NS093435)
Role: Co-Investigator
Time Commitment: 0.36 calendar months
Support Agency: National Institutes of Health
Funding Agency Grants officer:
Margaret Sutherland
NIH/NINDS
Neuroscience Center, Room 2222
6001 Executive Blvd MSC 9525
Bethesda, MD 20892-9525
Performance Period: 7/1/16 – 6/30/18
Annual Direct Costs: $150,000
Project Goals: The major goals of this project are to determine if α-Gal A deficiency exacerbates α-syn-associated neurotoxicity and to determine if increasing α-Gal A activity attenuates α-syn-associated neurotoxicity.
Specific Aims:

Aim 1: Determine if α-Gal A deficiency exacerbates α-syn-associated neurotoxicity.
Aim 2: Determine if increasing α-Gal A activity attenuates α-syn-associated neurotoxicity.
Potential Overlap: None.

Active Support

Erik D. Roberson

Current Support

New support since last reporting
Title: BIN1, Interneuron Activity, and Network Dysfunction in Alzheimer's Disease (RF1AG059405)
Role: PI
Time Commitment: 4.2 calendar months
Support Agency: NIH
Funding Agency Grants officer:
Bradley Wise
GWY BG RM 3E515
7201 Wisconsin Ave
Bethesda, MD 20814
Performance Period: 6/15/18 –05/31/23
Annual Direct Costs: $348,896
Project Goals: The main goal of this project is to determine the function of neuronal BIN1 and determine a mechanism for the link between BIN1 and Alzheimer's disease.
Specific Aims:
Aim 1: To test the hypothesis that lower BIN1 levels reduce neuronal activity in both excitatory and inhibitory neurons, with contrasting effects on susceptibility to network hyperexcitability.
Aim 2: To test the hypothesis that lower BIN1 levels in parvalbumin-positive interneurons impair gamma oscillations and cognitive function.
Aim 3: To test the hypothesis that lower BIN1 levels in inhibitory neurons drive dysfunction in mouse models of AD.
Potential Overlap: None.

New support since last reporting
Title: Exosomal Changes in Progranulin FTD
Role: PI
Time Commitment: 1.2 calendar months
Support Agency: The Bluefield Project to Cure Frontotemporal Dementia
Funding Agency Grants officer:
Rodney Pearlman
1650 Owens St, Room 205
San Francisco, CA 94158
Performance Period: 1/1/18 – 12/31/19
Annual Direct Costs: $163,637
Project Goals: The major goal of this project is to identify mechanisms by which progranulin insufficiency causes neuronal dysfunction.
Specific Aims:
Aim 1: To determine if plasma exosomes from FTD-GRN patients contain increased levels of TDP-43.
Aim 2: To determine the therapeutic potential of the NMDA receptor coagonist cycloserine in progranulin-haploinsufficient mice.
Potential Overlap: None.

New support since last reporting
Title: Targeting Rho Kinases for Alzheimer's Disease Therapeutics (R01AG054719)
Role: PI
Time Commitment: 0.12 calendar months
Support Agency: NIH

Funding Agency Grants officer:
Austin Jyan-yu Yang
GWY BG RM 3E419
7201 Wisconsin Ave
Bethesda, MD 20814
Performance Period: 7/15/17 – 5/31/22
Annual Direct Costs: $250,000
Project Goals: The major goal of this project is to use pharmacologic and genetic approaches to test the hypothesis that Rho kinases are rational therapeutic targets to delay or prevent Alzheimer's disease.
Specific Aims:
Aim 1: Determine if Aβ-induced dendritic degeneration is mediated by ROCK1 or ROCK2.
Aim 2: Determine if pharmacologic inhibition of ROCKs is protective in AD mouse models.
Aim 3: Determine how autophagic degradation of tau is mediated by ROCKs.
Potential Overlap: None.

Title: A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of C2N-8E12 in Subjects with Progressive Supranuclear Palsy
Role: Site PI
Time Commitment: 0.18 calendar months
Support Agency: C2N Diagnostics
Funding Agency Grants officer:
Joel Braunstein, MD, MBA
C2N Diagnostics
Center for Emerging Technologies
4041 Forest Park Ave
St. Louis, MO
Performance Period: 10/1/15 – 9/30/19
Total Direct Costs: $149,459
Project Goals: The main goal of this project is to test the safety, tolerability, and pharmacokinetics of an investigational compound in patients with progressive supranuclear palsey.
Specific Aims:
Aim 1: The primary goal is to determine the safety, tolerability, and maximally tolerated dose (MTD) of a single dose of C2N-8E12.
Aim 2: The secondary objectives are to determine: (i) single-dose pharmacokinetics; (ii) penetration of C2N -8E12 into cerebrospinal fluid (CSF); and (iii) exploratory aim of biological target engagement through the measurement of soluble tau levels in blood and CSF.
Potential Overlap: None.

Title: Preclinical Testing of a Progranulin-Raising Therapeutic
Role: PI
Time Commitment: 0.6 calendar months
Support Agency: Alector LLC
Funding Agency Grants officer:
Performance Period: 04/01/16 – 06/30/19 extension with additional funds
Annual Direct Costs: $34,030
Project Goals: The goal of this proposal is to test the ability of an antibody to normalize brain progranulin levels and correct FTD-like behavior and neuronal dysfunction in a mouse model of FTD.
Potential Overlap: None.

Title: A Phase II/III Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of 2 Potential Disease Modifying Therapies in Individuals at Risk for and with Dominantly Inherited Alzheimer's Disease

Role: Site PI
Time Commitment: 0.8 calendar months
Support Agency: Washington University/Quintiles
Funding Agency Grants officer:
Nicole Rhodes
Sr. Clinical Trials Assistant
Quintiles Plaza
3rd Floor
4820 Emperor Blvd.
Durham, NC 27703
Performance Period: 11/22/13 – 11/21/20
Total Direct Costs: $841,355
Project Goals: The major goal of this study is to determine the efficacy of early treatment in carriers of autosomal dominant mutations causing Alzheimer's disease.
Specific Aims: To assess the safety, tolerability, biomarker and cognitive efficacy of gantenerumab and solanezumab in subjects who are known to have an Alzheimer's disease-causing mutation by determining if treatment with the study drug improves cognitive outcomes and disease-related biomarkers.
Potential Overlap: None.

Title: Reducing Tau as a Therapeutic Strategy for Improving Cognitive Dysfunction in Parkinson's Disease (W81XWH-16-1 -0677)
Role: Co-Investigator
Time Commitment: 0.36 calendar months
Support Agency: Department of Defense
Funding Agency Grants officer:
Karen L. Petrore
US Army Medical Research Acquisition Activity Assistance Branch – Building 843
820 Chandler St
Ft. Detrick, MD 21702
Performance Period: 9/15/16 – 3/14/19, no cost extension
Annual Direct Costs: No cost extension
Project Goals: The major goals are to test the following hypotheses: The absence of tau will 1) slow the spread of pathologic α-syn, and 2) prevent neuronal dysfunction and behavioral defects related to cognition and mood disorders that caused by these inclusions.
Specific Aims:
Aim 1: Determine if tau ablation inhibits spread of α-syn inclusions within the neuron and restores axonal transport defects produced by α-syn inclusions.
Aim 2: Determine if constitutive Tau knockout prevents the formation of α-syn inclusions either locally or in downstream brain regions and prevents behavioral defects produced by these inclusions.
Potential Overlap: This New Investigator Grant is using constitutive Tau Ko mice to examine if knocking out Tau prevents cognitive dysfunction, axonal transport defects and inclusion formation in brain areas relevant for cognition. It has served to generate feasibility data upon which we are basing our current grant. This grant will determine if reducing Tau after formation of synuclein inclusions prevent progression of pathology and behavioral phenotypes. Such findings would be more clinically relevant for Tau as a therapeutic since PD pathology initiates before patients are seen in the clinic.

Title: Imaging Dementia - Evidence for Amloid Scanning (IDEAS) Study: A Coverage with Evidence Development Longitudinal Cohort Study
Role: Site PI
Time Commitment: 0.12 calendar months
Support Agency: American College of Radiology
Funding Agency Grants officer:

Gil D. Rabinovici, M.D.
University of California, San Francisco
Performance Period: 4/21/2016 – 7/19/21
Total Direct Costs: $107,250
Project Goals: The main goal of this project is to establish an open label, longitudinal cohort study to assess the impact of amyloid PET on patient outcomes under Coverage with Evidence (CED) in patients meeting Appropriate Use Criteria (AUC) for amyloid PET.
Specific Aims:
Aim 1: To assess the impact of amyloid PET on the management of patients meeting Appropriate Use Criteria (AUC).
Aim 2: To assess the impact of amyloid PET on hospital admissions and emergency room visits in patients enrolled in the study cohort (amyloid PET-known) compared to matched patients not in the cohort (amyloid PET-naïve) over 12 months.
Potential Overlap: None.

New support since last reporting
Title: A Study to Model Rates of Change on Neuropsychological Test Measures in Subjects Diagnosed With Behavioral Variant Frontotemporal Dementia and Healthy Subjects
Role: Site PI
Time Commitment: 0.12 calendar months
Support Agency: Biogen Idec, Inc.
Funding Agency Grants officer:
Chris Henderson
Biogen MA Inc.
250 Binney Street
Cambridge, MA 02142
Performance Period: 7/24/17 – 7/23/21
Total Direct Costs: $44,659
Project Goals: The goal of this study is to identify cognitive measures predictive of bvFTD progression over a period of 12 months or less, and to estimate the effect size of this change.
Specific Aims:
Aim 1: Estimate the change in disease-related cognitive decline over 1 year on a battery of cognitive tests administered to subjects with early-stage symptomatic bvFTD phenotypic variant.
Aim 2: Identify the cognitive test or brief battery of cognitive tests which are the most sensitive to detect bvFTD progression.
Aim 3: Determine the optimal schedule of administration of cognitive tests to detect bvFTD progression.
Aim 4: Evaluate the relationship between cognitive tests and measures of behavior, function, caregiver's burden, and quality of life (QOL).
Aim 5: Obtain blood samples for genetic and exploratory biomarkers correlations.
Potential Overlap: None.

New support since last reporting
Title: A Randomized, Double-Blind, Placebo-Controlled Multiple Dose Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of ABBV-8E12 in Progressive Supranuclear Palsy
Role: Sub-investigator
Time Commitment: 0.12 calendar months
Support Agency: AbbVie, Inc.
Funding Agency Grants officer:
Susan Buttler
Dept. R479, Bldg. AP34
AbbVie Inc.
1 N Waukegan Rd

North Chicago, IL 60064
Performance Period: 4/12/17 – 4/11/22
Total Direct Costs: $324,909
Project Goals: The major goals of this study are to assess the efficacy of ABBV-8E12 in slowing disease progression in subjects with progressive supranuclear palsy as measured by the PSP Rating Scale (PSP-RS), and to assess the long term safety and tolerability of ABBV-8E12 for up to 52 weeks in subjects with progressive supranuclear palsy.
Specific Aims:
Aim 1: To assess the efficacy of ABBV-8E12 in slowing disease progression in subjects with progressive supranuclear palsy as measured by the PSP Rating Scale (PSP-RS).
Aim 2: To assess the long term safety and tolerability of ABBV-8E12 for up to 52 weeks in subjects with progressive supranuclear palsy.
Potential Overlap: None.

New support since last reporting
Title: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: Biogen, Inc.
Funding Agency Grants officer:
Thomas Goodin
14 Cambridge Center
Cambridge, MA 02142
Performance Period: 1/25/16 – 1/24/20
Total Direct Costs: $961,578
Project Goals: Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
The primary objective of the study is to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score as compared with placebo in subjects with early AD.
Potential Overlap: None.

New support since last reporting
Title: Improving Family Quality of Life through training to reduce care-resistant behaviors by people with Alzheimer Dementia and Traumatic Brain Injury (W81XWH-16-1-0527)
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: Department of Defense
Funding Agency Grants officer:
Elena G. Howell
Performance Period: 9/1/16 – 8/31/19
Total Direct Costs: $734,955
Project Goals: The goal of this project is to develop, implement, and assess the efficacy of a theoretically driven teaching/coaching intervention for reducing burden among caregivers of people with care resistant behavior-triggered behavioral and psychiatric symptoms of dementia and neuropsychiatric symptoms after traumatic brain injury.
Specific Aims:
Aim 1: Translate a theoretically-driven intervention, demonstrated to be effective for nursing home staff to reduce care resistant behaviors among people with dementia to a distance-learning education and coaching program for family caregivers of people with dementia or TBI.
Aim 2: Assess the efficacy of the intervention for reducing frequency or severity of CRB-triggered symptoms of agitation, aggression, and irritability.

Aim 3: Determine how patient and caregiver characteristics influence the effectiveness of the intervention.
Aim 4: Assess the efficacy of the intervention for improving qualityof life of patients, caregivers, and families.
Aim 5: Evaluate how the intervention affects the health care costs ofpeople with dementia or TBI.
Potential Overlap: None.

New support since last reporting
Title: A Multicenter, Open-Label, Long-Term Treatment Study of Intravenously Administered BMS-986168 in Patients with Progressive Supranuclear Palsy Who Participated in Study CN002003
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: Bristol Myers Squibb
Funding Agency Grants officer:
Michael Grundman
13236 Haxton Place
San Diego, CA 92130
Performance Period: 4/5/16 – 4/4/20
Total Direct Costs: $263,920
Project Goals: The goal of this study is to evaluate the long-term safety and tolerability of multiple intravenous (IV) infusions of BMS-986168 in patients with PSP.
Potential Overlap: None.

New support since last reporting
Title: A Multicenter, Open-Label, Long-Term Treatment Study of Intravenously Administered BIIB092 in Patients with Progressive Supranuclear Palsy Who Participated in Study CN002003
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: Biogen, Inc.
Funding Agency Grants officer:
Tina Olsson
225 Binney Street
Cambridge, MA 02142
Performance Period: 6/4/18 – 2/2/20
Total Direct Costs: $388,843
Project Goals: The primary objective of the study is to evaluate the long term safety and tolerability of multiple IV infusions of BIIB092 in patients with PSP.
Potential Overlap: None.

New support since last reporting
Title: A Phase 2b/3 Randomized, Double-blind, Placebo-Controlled, Parallel Group, Multicenter Study Investigation the Efficacy and Safety of JNJ-54861911 in Subjects who are Asymptomatic at Risk for Developing Alzheimer's Dementia
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: Janssen Research and Development, LLC
Performance Period: 3/24/17 – 2/24/23
Total Direct Costs: $1,263,330
Project Goals: The primary objective of this study is to determine whether treatment with JNJ-54861911 slows cognitive decline compared with placebo treatment, as measured by a composite cognitive measure, the Preclinical Alzheimer Cognitive Composite, in amyloid-positive subjects who are asymptomatic at risk for developing Alzheimer's dementia.
Potential Overlap: None.

New support since last reporting
Title: Randomized, Double-blind, Parallel-Group, Placebo-Controlled, Dose Ranging Study of Piromelatine in Patients with Mild Dementia Due to Alzheimer's Disease
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: Neurim Pharmaceuticals
Funding Agency Grants officer:
Amnon Katz
27 Habarzel Street
Tel-Aviv 69710
Israel
Performance Period: 5/4/17 – 5/3/21
Total Direct Costs: $116,736
Project Goals: The primary goal of this study is to compare the effect of piromelatine (5, 20, and 50 mg) to that of placebo in the change from baseline in global composite score of the computerized Neuropsychological Test.
Potential Overlap: None.

New support since last reporting
Title: Longitudinal Evaluation of Amyloid Risk and Neurodegeneration - the LEARN Study: A companion observational study to Antl-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Trial
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: University of Southern California
Funding Agency Grants officer:
Michael Selsnik
950 Gilman Dr. #0934
La Jolla, CA 92093
Performance Period: 11/01/16 – 10/31/18
Total Direct Costs: No cost extension
Project Goals: The primary goal of this study is to characterize the longitudinal change on the cognitive, clinical, and biomarker measures used in the A4 trial in individuals who fall below the A4 threshold for evidence of elevated Amyloid (Aβne) based on the A4 screening PET scan in comparison to the A4 placebo arm individuals.
Potential Overlap: None.

New support since last reporting
Title: Alzheimer's Disease Cooperative Study – A4 Study
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: University of Southern California
Funding Agency Grants officer:
Michael Selsnik
950 Gilman Dr. #0934
La Jolla, CA 92093
Performance Period: 12/11/16 – 12/10/18
Total Direct Costs: $650,340
Project Goals: The primary objective of this study is to test the hypothesis that solanezumab, administered as an intravenous infusion at a dose of 400 mg every weeks for 3 years, will slow cognitive decline as compared with placebo in subjects with preclinical AD.
Potential Overlap: None.

New support since last reporting
Title: An Extension Study of ABBV-8E12 in Progressive Supranuclear Palsy (PSP)
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: Abbvie, Inc.
Funding Agency Grants officer:
Viola Meehan
Dept. R479, Bldg. AP34
AbbVie Inc.
1 N Waukegan Rd
North Chicago, IL 60064
Performance Period: 6/14/18 – 6/13/22
Total Direct Costs: $2,360,934
Project Goals: The primary objectives of this study are to assess the long-term safety and tolerability of ABBV-8E12 in subjects with PSP and to assess the long-term efficacy of ABBV-8E12 in slowing disease progression in subjects with PSP as measured by the PSP Rating Scale (PSPRS).
Potential Overlap: None.

New support since last reporting
Title: Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, and Efficacy of BIIB092 in Subjects with Mild Cognitive Impairment due to Alzheimer's Disease or with Mild Alzheimer's Disease
Role: Sub-investigator, backup
Time Commitment: 0.01 calendar months
Support Agency: Biogen MA, Inc.
Funding Agency Grants officer:
Carole Springfield
10188 Telesis Ct, Ste 400
San Diego, CA 92121
Performance Period: 8/1/18 – 7/31/22
Total Direct Costs: $338,273
Project Goals: The primary objective of the study is to evaluate the safety and tolerability of BIIB092 in subjects with MCI due to AD or with mild AD.
Potential Overlap: None.

Support ended since previous reporting

Title: Causes, Treatment, and Prevention of Corticobasal Degeneration
Role: Site PI
Time Commitment: 0.36 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 extension
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.

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: Site PI
Time Commitment: 0.24 calendar months
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 – 9/30/18
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: Therapeutic Strategies in Mouse Models of FTD Due To Progranulin Insufficiency
Role: PI
Time Commitment: 2.4 calendar months
Support Agency: Consortium for Frontotemporal Dementia Research/ The Bluefield Project to Cure Frontotemporal Dementia
Funding Agency Grants officer:
Rodney Pearlman
1650 Owens St, Room 205
San Francisco, CA 94158
Performance Period: 1/1/15 – 12/31/17
Annual Direct Costs: $246,770
Project Goals: The first goal of this project is to extend our initial studies of AAV-progranulin to address key preclinical questions about the effectiveness of progranulin gene transfer. Second, building on the identification of behavioral deficits in Grn+/– mice similar to those we found in tau mice, we will determine if the efficacy of cycloserine that we identified in tau mice is also seen in progranulin mice.
Specific Aims:
Aim 1: To determine the therapeutic potential of progranulin gene transfer in progranulin-haploinsufficient mice.
Aim 2: To determine the therapeutic potential of the NMDA receptor coagonist cycloserine in progranulin-haploinsufficient mice.
Potential Overlap: None.

Title: Development of Inhibitors of the Tau-Fyn Interaction for the Treatment of Alzheimer's Disease
Role: PI
Time Commitment: 0.6 calendar months
Support Agency: BrightFocus Foundation
Funding Agency Grants officer:
Stacy Ragos Haller
BrightFocus Foundation
22512 Gateway Center Dr
Clarksburg, MD 20871
Performance Period: 7/1/15 – 6/30/18
Annual Direct Costs: $88,737
Project Goals: The major goal of this project is to develop a small molecule inhibitor of the interaction between the microtubule-associated protein Tau and the Src-family tyrosine kinase Fyn.
Specific Aims:
Aim 1: Determine the ability of the prioritized hits from our high-throughput Tau–Fyn interaction inhibitor assay to reduce Aβ toxicity in primary neurons, and execute a structure-activity relationship (SAR) study on confirmed hit compounds from which lead optimization on a select chemical series(s) can be initiated (Year 1).
Aim 2: Using a hypothesis-driven medicinal chemistry lead optimization program, identify 2–3 novel inhibitors of the Tau–Fyn interaction as probe compounds (Year 2), and determine pharmacokinetic (PK) profiles on lead molecules in order to assess which compounds have preferred drug-like properties and are most worthy of in vivo testing (Year 3).
Potential Overlap: None.

Title: Advancing Research and Treatment for Frontotemporal Lobar Degeneration [ARTFL]: Research Project 1 & 2
Role: Site PI
Time Commitment: 0.12 calendar months
Support Agency: University of California, San Francisco
Funding Agency Grants officer:
Rodney Pearlman
1650 Owens St, Room 205
San Francisco, CA 94158
Performance Period: 05/01/15 – 07/31/17
Total Direct Costs: $149,459
Project Goals: The main goal of this project is to test the safety, tolerability, and pharmacokinetics of an investigational compound in patients with progressive supranuclear palsey.
Specific Aims:
Aim 1: To build a reliable FTLD clinical research network to support treatment and prevention clinical trials.
Aim 2: To determine the clinical characteristics of sporadic FTLD syndromes in patients who would meet typical clinical trial eligibility criteria, and the barriers to clinical trial participation.
Aim 3: To develop a familial FTLD cohort for clinical trials and biomarker studies.
Potential Overlap: None.

Active Support

Thomas van Groen

Current Support

Title: UAB Neuroscience Core Center Grant; CORE A (Behavioral Assessment Core)
Role: Technical Director of Behavioral Assessment Core
Time Commitment: 3.0 calendar months
Support Agency: NIH P30 NS47466 (Hablitz, PI)
Funding Agency Grants officer:
Talley, Edmund M
NIH/NINDS
Neuroscience Center, Room 2223
6001 Executive Blvd, MSC 9525
Bethesda, MD 20892-9525
Performance Period: 12/01/10 – 11/30/19
Annual Direct Costs: $119,776
Project Goals: The Behavioral Assessment Core (Core A) provides both service-oriented behavioral phenotyping and research staff training to investigators using rodents**.**
Potential Overlap: None.

Title: Reducing Tau as a Therapeutic Strategy for Improving Cognitive Dysfunction in Parkinson's Disease (W81XWH-16-1 -0677)
Role: Collaborator
Time Commitment: 0.078 calendar months (1% of 0.65 FTE)
Support Agency: Department of Defense
Funding Agency Grants officer:
Karen L. Petrore
US Army Medical Research Acquisition Activity Assistance Branch – Building 843
820 Chandler St
Ft. Detrick, MD 21702
Performance Period: 9/15/16 – 9/14/18
Annual Direct Costs: $124,994
Project Goals: The major goals are to test the following hypotheses: The absence of tau will 1) slow the spread of pathologic α-syn, and 2) prevent neuronal dysfunction and behavioral defects related to cognition and mood disorders that caused by these inclusions.
Specific Aims:
Aim 1: Determine if tau ablation inhibits spread of α-syn inclusions within the neuron and restores axonal transport defects produced by α-syn inclusions.
Aim 2: Determine if constitutive Tau knockout prevents the formation of α-syn inclusions either locally or in downstream brain regions and prevents behavioral defects produced by these inclusions.
Potential Overlap: None.

Support ended since last reporting

Title: SULT4A1 in Zebrafish Development
Role: Collaborator
Time Commitment: 0.6 calendar months
Support Agency: NIH R01 GM113980-01 (Falany, PI)

Funding Agency Grants officer:
Okita, Richard T NIH/NIA
National Institute on Aging
31 Center Drive, MSC 2292
Bethesda, MD 20892-9525
Performance Period: 03/01/15 – 02/28/18
Annual Direct Costs: $175,800
Project Goals: The overall goal of this proposal is to establish the regulation and function of sulfotransferase (SULT) 4A1 during development and in adults in the genetically tractable zebrafish (Danio rerio) model system.
Specific Aims:
Aim1: 1) To investigate the effects of disrupting SULT4A1 activity or expression on zebrafish development. Analysis of morphological characteristics of embryos and adults, gene expression, and reproduction will be carried out in the TALEN-derived SULT4A1 mutants.
Aim 2: To identify behavioral phenotypes in larval and adult SULT4A1 active site deletion and knockout zebrafish. Vision and behavioral studies will be performed to generate insights into the neural effects of SULT4A1 dysfunction.
Aim 3: To analyze the role of SULT4A1 in phototransduction in the zebrafish.
Potential Overlap: None.