OMB Number: 4040-0001
Expiration Date: 6/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

3. DATE RECEIVED BY STATE:

State Application Identifier:

1. TYPE OF SUBMISSION

☐ Pre-application ☒ Application ☐ Changed/Corrected Application

2. DATE SUBMITTED:

Applicant Identifier:

4. a. Federal Identifier: F32NS090678

b. Agency Routing Identifier:

c. Previous Grants.gov Tracking ID:

5. APPLICANT INFORMATION

Organizational DUNS: 063690705

Legal Name: University of Alabama at Birmingham

Department: Office of Sponsored Programs

Division:

Street1: 1720 2nd Ave. S., AB 1170

Street2:

City: Birmingham

County / Parish: Jefferson

State: AL: Alabama

Province:

Country: USA: UNITED STATES

ZIP / Postal Code: 352940111

Person to be contacted on matters involving this application

Prefix: Ms.

First Name: Ashley

Middle Name:

Last Name: Davis

Suffix:

Position/Title: Grants and Contracts Officer

Street1: 1720 2nd Ave S, AB 1170

Street2:

City: Birmingham

County / Parish: Jefferson

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Province:

Country: USA: UNITED STATES

ZIP / Postal Code: 352940111

Phone Number: 205-996-6956

Fax Number: 205-975-5977

Email: ashleydav@uab.edu

6. EMPLOYER IDENTIFICATION *(EIN) or (TIN):* 1636005396A6

7. TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION:

☐ New ☒ Resubmission

☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).

☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration

☐ E. Other (specify):

Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

Mechanisms of frontotemporal dementia like behavior in progranulin deficient mice

12. PROPOSED PROJECT:

Start Date: 04/01/2015

Ending Date: 03/31/2017

13. CONGRESSIONAL DISTRICT OF APPLICANT: AL-007

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name: Andrew Middle Name:
Last Name: Arrant Suffix: Ph.D
Position/Title: Postdoctoral Fellow
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Phone Number: 205-996-9435 Fax Number: 205-996-9436
Email: aearrant@uab.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	109,666.00
b. Total Non-Federal Funds	0.00
c. Total Federal & Non-Federal Funds	109,666.00
d. Estimated Program Income	0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR
☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious. or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

☒ **I agree**

The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL (Disclosure of Lobbying Activities) or other Explanatory Documentation

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: Ms. First Name: Lynn Middle Name:
Last Name: Stedman Suffix: MBA
Position/Title: Director, Office of Sponsored Programs
Organization: University of Alabama at Birmingham
Department: Office of Sponsored Programs Division:
Street1: 1720 2nd Ave. S., AB 1170
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Country: USA: UNITED STATES ZIP / Postal Code: 352940111
Phone Number: 205-934-5266 Fax Number: 205-9755977
Email: osp@uab.edu

Signature of Authorized Representative: Completed on submission to Grants.gov

Date Signed: Completed on submission to Grants.gov

20. Pre-application Add Attachment | Delete Attachment | View Attachment

21. Cover Letter Attachment Cover Letter.pdf Add Attachment | Delete Attachment | View Attachment

August 8, 2014

To Whom It May Concern:

The attached application, entitled “Mechanisms of Frontotemporal Dementia-like Behavior in Progranulin-Deficient Mice” is submitted for the Ruth L. Kirschstein NRSA F32 fellowship, program announcement number PA-14-149.

Please assign this application to:

Institute/Center
National Institute of Neurological Disorders and Stroke – NINDS
National Institute for Aging – NIA

Scientific Review Group:
Brain Disorders, Language, Communication, and Related Neurosciences Fellowship Study Section – F01

My references are listed below:

1.) Name: Cynthia Kuhn
Degree: PhD
Title: Professor
Affiliation: Dept. of Pharmacology & Cancer Biology, Duke University

2.) Name: Theodore Slotkin
Degree: PhD
Title: Professor
Affiliation: Dept. of Pharmacology & Cancer Biology, Duke University

3.) Name: Edward Levin
Degree: PhD
Title: Professor
Affiliation: Dept. of Psychiatry & Behavioral Sciences, Duke University

Thank you for your consideration.

Sincerely,

Andrew Arrant

PHS Fellowship Supplemental Form

OMB Number: 0925-0001

A. Application Type:

From SF424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated here for your reference as you provide the responses that are appropriate for this Fellowship application.

☐ New ☒ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

B. Research Training Plan

1. Introduction to Application *(for RESUBMISSION applications only)*	Introduction.pdf	Add Attachment	Delete Attachment	View Attachment
2. * Specific Aims	Specific Aims.pdf	Add Attachment	Delete Attachment	View Attachment
3. * Research Strategy	Research Strategy.pdf	Add Attachment	Delete Attachment	View Attachment
4. Progress Report Publication List *(for RENEWAL applications only)*		Add Attachment	Delete Attachment	View Attachment

Human Subjects

Please note. The following item is taken from the Research & Related Other Project Information form. The response provided on that page, regarding the involvement of human subjects, is repeated here for your reference as you provide related responses for this Fellowship application. If you wish to change the answer to the item shown below, please do so on the Research & Related Other Project Information form; you will not be able to edit the response here.

Are Human Subjects Involved? ☐ Yes ☒ No

5. Human Subjects Involvement Indefinite?	☐ Yes	☐ No	
6. Clinical Trial?	☐ Yes	☐ No	
7. Agency-Defined Phase III Clinical Trial?	☐ Yes	☐ No	

8. Protection of Human Subjects		Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Women and Minorities		Add Attachment	Delete Attachment	View Attachment
10. Inclusion of Children		Add Attachment	Delete Attachment	View Attachment

Other Research Training Plan Sections

Please note. The following item is taken from the Research & Related Other Project Information form. The response provided on that page, regarding the use of vertebrate animals, is repeated here for your reference as you provide related responses for this Fellowship application. If you wish to change the answer to the item shown below, please do so on the Research & Related Other Project Information form; you will not be able to edit the response here.

Are Vertebrate Animals Used? ☒ Yes ☐ No

11. Vertebrate Animals Use Indefinite?	☐ Yes	☒ No		

12. Vertebrate Animals	Vertebrate Animals.pdf	Add Attachment	Delete Attachment	View Attachment
13. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
14. Resource Sharing Plan	Resource Sharing Plan.pdf	Add Attachment	Delete Attachment	View Attachment
15. * Respective Contributions	Respective Contributions.pdf	Add Attachment	Delete Attachment	View Attachment
16. * Selection of Sponsor and Institution	Selection of Sponsors and Institut	Add Attachment	Delete Attachment	View Attachment
17. * Responsible Conduct of Research	RCR.pdf	Add Attachment	Delete Attachment	View Attachment

Introduction

We appreciate the reviewers' constructive comments. All reviewers were enthusiastic about both the applicant and the institution, listing no weaknesses to address. The reviewers were satisfied with my productivity, and since the original submission I have had a co-author publication accepted and have begun preparing two first-author publications based on work from my T32 fellowship. The sponsor, Dr. Roberson, was also viewed positively, but there was concern over his limited experience in training postdoctoral fellows, as he started his lab at UAB in 2008. All reviewers felt that this inexperience lowered the training potential of the proposal, and suggested the addition of a senior co-sponsor. In response, we have invited Dr. David Standaert to serve as a co-sponsor. Dr. Standaert is chair of the Department of Neurology at UAB, and came from Massachusetts General/Harvard Medical School in 2006 to found the new Center for Neurodegeneration and Experimental Therapeutics. He has extensive training experience, having sponsored three postdoctoral fellows on NIH F awards and six on NIH K awards. We think that Dr. Standaert's mentorship will greatly enhance this proposal's training potential. We have also made other modifications to the training plan to customize it for my needs.

The reviewers felt that the research plan investigated an important topic, and requested more information on the rationale for investigating the mTOR pathway. They also made suggestions to improve the experimental design. In addition to explaining our rationale for investigating mTOR, we have adopted reviewer suggestions on the mTOR time course (Aim 1, subaim 1), and a pilot experiment to optimize the rapamycin dose (Aim 1, subaim 2). We have also provided the requested details in the Vertebrate Animals section on the power analysis used to determine animal numbers. In response to requests for more information on AAV injection titers, we have added data from several AAV titers showing the spread of infection and total progranulin levels in prefrontal cortex and amygdala. Finally, we have included exciting preliminary data showing that AAV-*Grn* reverses the social dominance phenotype of 12-month-old *Grn*$^{+/-}$ mice. We are excited about these data as they show correction of deficits by AAV-*Grn* after the onset of abnormal behavior. We think that this increases the likelihood of completing these studies in two years, which was a concern of one reviewer.

Additional issues listed by the reviewers are addressed below. Significant changes to the proposal are marked with a line in the left margin.

1. "…it must be acknowledged that this animal model does not faithfully recapitulate FTD with GRN mutations…and thus the findings may not directly translate to the human disease." - Reviewer 1

We definitely acknowledge this limitation, which is essentially a universal issue with mouse models. However, despite not recapitulating all aspects of disease, mouse models have still been able to provide useful insight into a variety of neurodegenerative disorders (2-6). FTD-related *GRN* mutations cause *GRN* haploinsufficiency, a state that is modeled in *Grn*$^{+/-}$ mice. Despite the lack of TDP43 aggregates and neuronal loss, *Grn*$^{+/-}$ mice develop abnormal behavior and amygdala dysfunction that may model core features of FTD. *Grn*$^{+/-}$ mice may therefore be more relevant to the early stages of FTD, before the progression to severe atrophy and neuronal loss. There is much more that can be said about this important issue, and within space constraints, we have added some discussion in the Research Strategy.

2. "The major weakness of the research plan is a lack of understanding of how the authors came to focus on mTor." – Reviewer 2

Our interest in mTOR began with a report of decreased S6K2 levels in iPSC-derived neurons from FTD-*GRN* patients, and was further heightened by reports of reduced p-S6K1 in young (8-10 week old) *Grn*$^{-/-}$ mice, and interaction of progranulin with IGF-1 in cell culture (7-11). We discuss this further in the Research Strategy.

3. "In vivo AAV work is ABSL2 and should be discussed." – Reviewer 2

Our AAV-*Grn* vector does not express a toxic or oncogenic gene and is thus handled under ABSL1 conditions based on NIH and UAB guidelines.

4. "The applicant has worked in a similar research area (neuropharmacology) before. Therefore the training plan… has to specify how the fellowship will significantly train the post-doc in new fields." – Reviewer 3

There is very little overlap between the conceptual and technical approaches of my graduate work and the current proposal. Conceptually, my graduate research focused on neurochemistry, addiction, risk taking, and adolescent development. The current proposal studies the neurobiology of a neurodegenerative disease. Technically, my graduate work utilized approaches such as anxiety testing, *in vivo* microdialysis, and HPLC. The current proposal involves mouse genetics, tests of social behavior and fear memory, biochemistry, and molecular biology. The current proposal will provide me with conceptual training in neurodegeneration and new technical skills that will facilitate my goal of becoming an independent scientist in the field of neurodegeneration.

Specific Aims

Frontotemporal dementia (FTD) is a progressive, fatal neurodegenerative disorder in which the frontal and temporal lobes of the brain degenerate, resulting in behavioral changes such as disinhibition and social withdrawal. FTD is the second most common cause of dementia after Alzheimer's disease, and may be as common as Alzheimer's prior to age 65. There is currently no treatment for FTD. Mutations in progranulin (*GRN*) are one of the major genetic causes of FTD, accounting for 5–10% of all FTD cases and around 25% of familial cases. Progranulin is a secreted glycoprotein that has neurotrophic and anti-inflammatory effects in the brain. All known FTD-related *GRN* mutations are loss-of-function mutations, so it is thought these mutations cause FTD through progranulin deficiency.

Grn$^{+/-}$ and *Grn*$^{-/-}$ mice have been developed as an animal model of progranulin deficiency, and exhibit FTD-like behavioral abnormalities and neuronal dysfunction. *Grn*$^{+/-}$ and *Grn*$^{-/-}$ mice develop abnormal social behavior, conditioned fear deficits, and amygdala dysfunction by 6-7 months of age. *Grn*$^{-/-}$, but not *Grn*$^{+/-}$ mice, also develop gliosis and inflammation, suggesting that inflammation does not cause the behavioral deficits and amygdala dysfunction. The mechanism behind the abnormal behavior and amygdala dysfunction remains unknown, and is a major gap in our understanding of how progranulin deficiency disrupts neuronal function.

We investigated the mTOR pathway as a potential mechanism for the phenotype of progranulin-deficient mice based on reports of altered S6 kinase expression and phosphorylation in progranulin-deficient model systems, and of interaction of progranulin with insulin/IGF-1 signaling. We found increased phosphorylation of Akt and ribosomal protein S6 in the amygdala of *Grn*$^{+/-}$ mice relative to wild-type, which suggests increased signaling through the mTOR pathway. Elevated mTOR signaling causes abnormal social behavior in several genetic mouse models of autism, and mTOR signaling may also be involved in conditioned fear memory. **We therefore hypothesize that progranulin deficiency causes abnormal social behavior, conditioned fear, and amygdala dysfunction through elevated mTOR signaling.** We propose to investigate this hypothesis with the following specific aims.

Aim 1 – To determine if increased mTOR signaling causes abnormal behavior and amygdala dysfunction in progranulin-deficient mice.

Subaim 1 – To investigate the anatomic and temporal association of increased mTOR signaling with abnormal behavior and amygdala dysfunction.

We hypothesize that elevated mTOR signaling might develop during the transition to abnormal behavior in *Grn*$^{+/-}$ mice (around 6-7 months), and in FTD-associated brain regions. We will test this hypothesis by western blotting for phospho-S6 (Ser235/236 & Ser240/44), phospho-S6 kinase (Thr389), phospho-Akt (Ser473), and phospho-mTOR (Ser2448) in FTD-associated brain regions (amygdala and prefrontal cortex) and a region not expected to be affected (cerebellum) in *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice at ages before (3 months), during (5 and 7 months), and after (9 months) the transition to abnormal behavior. We will also immunostain for these proteins to achieve finer anatomic resolution, and will perform co-staining for neuronal and glial markers.

Subaim 2 – *To determine if inhibiting mTOR signaling will prevent or reverse abnormal behavior and amygdala dysfunction in progranulin-deficient mice.*

If progranulin deficiency causes abnormal behavior and amygdala dysfunction through elevated mTOR signaling, then inhibiting mTOR signaling should normalize these deficits. We will test this hypothesis by treating *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice with rapamycin before (age 5-6 months) or after (age 9-12 months) the emergence of abnormal behavior. After performing a pilot study to optimize the rapamycin dose, the mice will be fed a control diet or a diet with rapamycin for four weeks prior to testing. We will test the mice in the tube test for social dominance and the three-chamber sociability test, followed by testing for conditioned fear. We will then expose the mice to a novel, social environment and measure amygdala activation using c-Fos immunostaining. Inhibition of mTOR signaling will be confirmed by western blotting of cortex and amygdala.

Aim 2 – To determine if restoring progranulin to progranulin-deficient mice will normalize both mTOR signaling and abnormal behavior.

If progranulin deficiency causes abnormal behavior and amygdala dysfunction through elevated mTOR signaling, then raising progranulin levels should normalize all of these phenotypes in progranulin-deficient mice. We will test this hypothesis by infusing AAV-*Grn* or AAV-*Gfp* into the amygdala and prefrontal cortex of *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice before (5-6 months) or after (9-12 months) the onset of abnormal behavior. Four weeks later, we will test the mice for social behavior, conditioned fear, and amygdala dysfunction as described in aim 1. mTOR signaling in cortex and amygdala samples will be measured by western blot.

Research Strategy

Significance

FTD is a fatal, progressive neurodegenerative disorder with a median age of onset in the 50s (12-14). FTD is the second most common cause of dementia after Alzheimer's disease (AD), and may be as common as AD in individuals under age 65 (12). There are multiple FTD subtypes, the most common of which is behavioral variant FTD, which is diagnosed based on signs such as social withdrawal, disinhibition, and loss of empathy (15). There are also several classes of FTD pathology based on the protein aggregates examined post-mortem. The two major classes include 90% of FTD patients, who have aggregates positive for either tau or the RNA binding protein TDP43 (16). It is currently unknown if or how these aggregates contribute to disease.

Genetics are a major cause of FTD, as 40-50% of cases are familial (17, 18). There are seven known genetic causes of FTD, with mutations in tau (*MAPT*), progranulin (*GRN*), and *C9ORF72* being the most common (19). *GRN* mutations account for 5-10% of all FTD cases, and all FTD-*GRN* cases have TDP43-positive protein aggregates (20). All FTD-related *GRN* mutations are loss-of-function mutations, so it is thought that progranulin deficiency may cause FTD-*GRN* (20-26). Progranulin-deficient mice ($Grn^{+/-}$ and $Grn^{-/-}$) have supported this hypothesis. $Grn^{+/-}$ and $Grn^{-/-}$ mice develop abnormal social and emotional behavioral by age 6-7 months that may model that seen in FTD (Fig.1a-c) (1, 27-29). These behavioral deficits are associated with amygdala dysfunction, as exposure of $Grn^{+/-}$ and $Grn^{-/-}$ mice to a novel, social environment produces less activation of the central amygdala than wild-type mice (Fig.1d) (1). This amygdala dysfunction may model disrupted connectivity in FTD patients' salience network, which includes the amygdala (30).

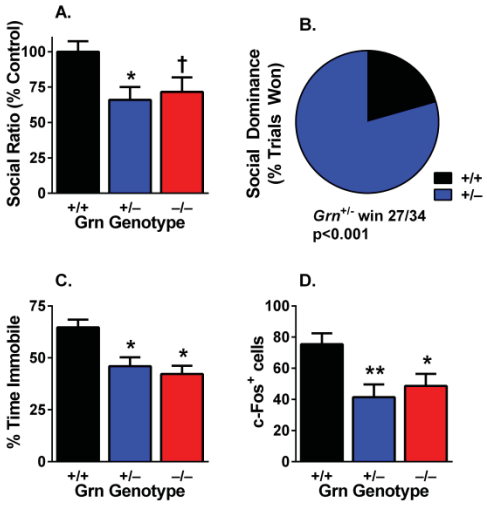

Figure 1: $Grn^{+/-}$ and $Grn^{-/-}$ mice have reduced social behavior in the 3 chamber sociability test (A.), increased social dominance in the tube test that progresses to less dominance with age (B.), and lower cued conditioned fear (C.). $Grn^{+/-}$ and $Grn^{-/-}$ mice also exhibit reduced central amygdala activation in a novel, social environment (D.). †=0.051, *=p<0.05, and **=p<0.01 by Dunnet's post-hoc test. These data are taken from reference (1).

A key consideration in working with progranulin-deficient mice is the degree to which $Grn^{+/-}$ and/or $Grn^{-/-}$ mice are a useful model of FTD-*GRN*. $Grn^{+/-}$ mice directly model the genetic insult in FTD-*GRN*, as all FTD-related *GRN* mutations are loss-of–function mutations that cause progranulin haploinsufficiency. $Grn^{-/-}$ mice are a less valid genetic model of FTD, as individuals homozygous for loss-of–function *GRN* mutations develop neuronal ceroid lipofuscinosis in their early twenties (31, 32). Similarly, $Grn^{-/-}$ mice develop lipofuscinosis that progresses with age (1, 9, 28, 29, 33-35). However, $Grn^{-/-}$ mice may be useful for modeling FTD-like pathology. $Grn^{-/-}$, but not $Grn^{+/-}$ mice, develop progressive inflammation and gliosis that becomes detectable by around 6 months of age, as well as increased phosphorylated TDP43, cytoplasmic TDP43 aggregates, and thalamic neuronal loss at age 20-23 months (1, 9, 28, 29, 33-36). This FTD-like pathology is clearly not required for abnormal behavior and amygdala dysfunction, as $Grn^{+/-}$ mice do not have any detectable pathology. Therefore, while neither $Grn^{+/-}$ nor $Grn^{-/-}$ mice recapitulate all aspects of FTD-*GRN*, both lines model several core aspects of the disease, including abnormal behavior, dysfunction in salience network regions (amygdala), and in the case of $Grn^{-/-}$ mice, some FTD-like pathology. Given the potentially confounding presence of lipofuscinosis in $Grn^{-/-}$ mice, we will use $Grn^{+/-}$ mice to investigate the molecular mechanisms by which progranulin deficiency disrupts neuronal function and behavior.

A major gap in our understanding of FTD-*GRN* is the mechanism by which progranulin deficiency causes neuronal dysfunction. Progranulin is expressed in neurons and microglia in the brain, where it likely has neurotrophic and anti-inflammatory effects (34, 37-39). The loss of either of these functions could lead to FTD. Unfortunately, the receptors and signaling pathways through which progranulin mediates these effects are poorly understood. The two most studied progranulin receptors are sortilin and TNF receptors. Sortilin facilitates progranulin uptake into cells, but this may simply be a trafficking mechanism as there is no evidence for activation of downstream signaling pathways and sortilin is not required for progranulin's neurotrophic effects (39, 40). Progranulin has also been reported to modulate inflammation as an antagonist of TNF receptors, but this finding has not been replicated in other studies (41-44). A greater understanding of the

mechanism by which progranulin deficiency causes neuronal dysfunction could facilitate discovery of new therapies, and could also reveal mechanisms that apply to other FTD subtypes.

We set out to elucidate the molecular mechanisms by which progranulin deficiency causes neuronal dysfunction by investigating whether disrupted cellular signaling is associated with abnormal behavior and amygdala dysfunction in *Grn*$^{+/-}$ mice. We became interested in the mTOR pathway based on abnormalities in S6 kinase in progranulin-deficient models. Neurons derived from stem cells taken from FTD-*GRN* patients have reduced total levels of S6K2, and young (8-10 week old) *Grn*$^{-/-}$ mice have reduced phosphorylated S6K1 in the cortex (7, 11). S6K1 and S6K2 are major downstream targets of mTOR that activate signaling cascades that modulate a variety of cell processes including protein synthesis and cell growth (45). There are also several reports of interaction of progranulin with insulin/IGF-1 signaling, which activates mTOR through Akt (46). Progranulin is able to substitute for IGF-1 in promoting proliferation of mouse fibroblasts, and stimulates growth of myoblasts incubated with an IGF-1R antagonist (8, 10). Progranulin's stimulation of myoblast growth is mTOR-dependent, as it is blocked by rapamycin (8). There may also be an interaction of progranulin with IGF-1 signaling in mouse brain, as 18 month old *Grn*$^{-/-}$ mice have elevated Igf1 mRNA levels in the brain (9). These data collectively indicate that progranulin is able to activate mTOR in a similar manner as IGF-1 in various cell types, and that progranulin deficiency results in dysregulated IGF-1/mTOR signaling. These data led us to conduct preliminary experiments that indicated increased mTOR signaling in *Grn*$^{+/-}$ mice.

The goal of this proposal is to use *Grn*$^{+/-}$ mice to investigate the hypothesis that progranulin deficiency causes neuronal dysfunction and abnormal behavior through elevated mTOR signaling. We developed this hypothesis based on the following preliminary data, and this idea is supported disruption of social behavior by elevated mTOR signaling in mouse models of autism (47-49). Successful completion of the proposed aims would advance FTD research on several fronts. First, these studies would provide the first evidence of a signaling pathway by which progranulin deficiency disrupts neuronal function and behavior, which would highlight the mTOR pathway for further investigation in FTD patients. These studies could also provide the first preclinical data for potential FTD-*GRN* therapies using an *in* vivo model, as we will test our hypothesis by attempting to correct the abnormal behavior of *Grn*$^{+/-}$ mice by inhibiting mTOR signaling with rapamycin and by increasing progranulin expression with an AAV vector. Both approaches could be readily translatable to FTD patients as rapamycin is already clinically approved for other uses, and multiple laboratories are engaging in efforts to devise practical strategies for increasing progranulin levels in humans (50, 51).

Preliminary Data

We began investigating the mTOR pathway by performing western blots for mTOR signaling molecules in the amygdala of 7-10 month old *Grn*$^{+/-}$ mice. We focused on *Grn*$^{+/-}$ mice due to the potentially confounding presence of lipofuscinosis in *Grn*$^{-/-}$ mice, and sampled the amygdala based on prior data indicating dysfunction in this brain region (Fig.1d) (1). We measured levels of phosphorylated ribosomal protein S6 (Ser 235/236) and phospho-Akt (Ser473) to assess molecules both downstream (p-S6) and upstream (p-Akt) of mTOR, and observed increased phosphorylation of both signaling molecules in *Grn*$^{+/-}$ mice relative to wild-type (Fig. 2a,b). These data suggest increased mTOR signaling in *Grn*$^{+/-}$ mice. The inconsistency with a prior report in 8-10 week old *Grn*$^{-/-}$ mice may be due to the age of the animals; a factor which we will investigate in the proposed experiments (7).

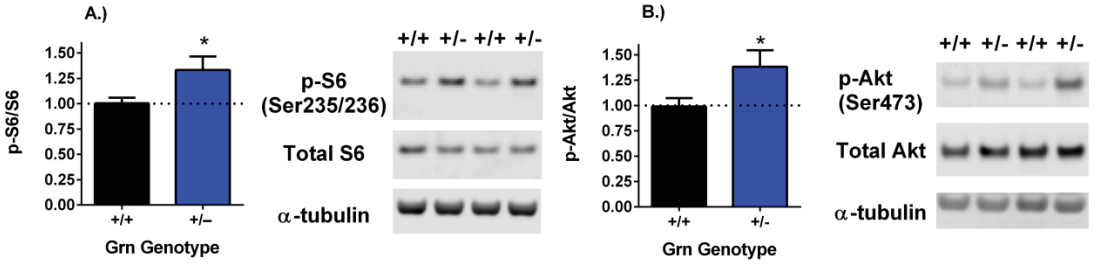

Figure 2: Elevated phosphorylation of ribosomal protein S6 (Ser235/236) (A.) and Akt (Ser473) (B.) in the amygdala of *Grn*$^{+/-}$ mice.

In another set of preliminary studies, we designed an AAV-*Grn* vector and tested its ability to express progranulin in mouse brain. We designed an AAV 2/1 vector to express mouse progranulin with a myc tag at the C terminus. Initial characterization of the vector in cell culture revealed that it expresses progranulin that is secreted normally (data not shown). Subsequent pilot studies in mouse brain showed that the virus robustly expresses progranulin in both amygdala and prefrontal cortex (Fig. 3).

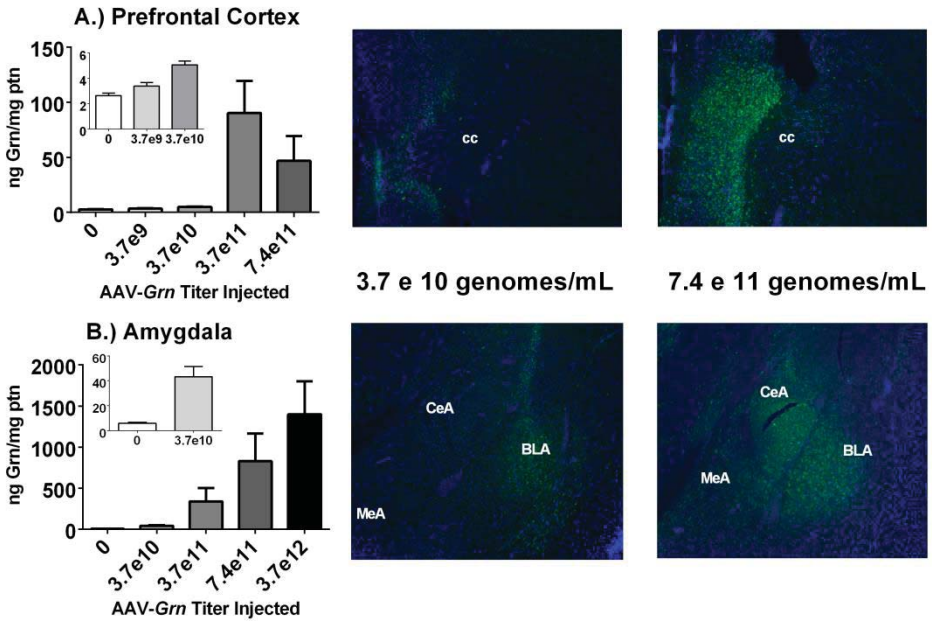

Figure 3: Optimization of AAV-*Grn* injection titers. Multiple titers of AAV-*Grn* were injected into prefrontal cortex (A.) or amygdala (B.), and brains were collected 2-4 weeks later for assessment of progranulin expression. Progranulin protein levels were assessed in each region by ELISA, and the spread of AAV infection was determined by immunostaining for the myc tag (green) on virally expressed progranulin. Uninjected wild-type mice were used as controls. Insets depict the lower three bars in A. and lower two bars in B. cc = corpus callosum, BLA = basolateral amygdala, CeA = central amygdala, MeA = medial amygdala

We then conducted a pilot behavioral study to determine if injection of an AAV-*Grn* titer that produces widespread infection and high progranulin levels (7.36e11 genomes/mL) would reverse abnormal behavior in 12 month old $Grn^{+/-}$ mice. Prior to AAV injection, the $Grn^{+/-}$ mice had a losing phenotype in the tube test for social dominance (Fig. 4a), which we typically observe at this age. We then injected the mice with AAV-*Gfp* or AAV-*Grn* into both the prefrontal cortex and amygdala (1 µL in each region, viral titer=7.36e11 genomes/mL), and allowed the mice to recover for four weeks prior to testing. We then tested the mice again in the tube test for social dominance. When paired with wild-type mice injected with AAV-*Gfp*, $Grn^{+/-}$ mice injected with AAV-*Gfp* still exhibited a losing phenotype (Fig. 4b). However, AAV-*Grn*–injected $Grn^{+/-}$ mice did not have a significant phenotype versus wild-type mice injected with either AAV-*Gfp* (Fig. 4c) or AAV-*Grn* (Fig. 4d). These data indicate that dual infusion of AAV-*Grn* into the amygdala and prefrontal cortex is capable of normalizing the social dominance phenotype of $Grn^{+/-}$ mice.

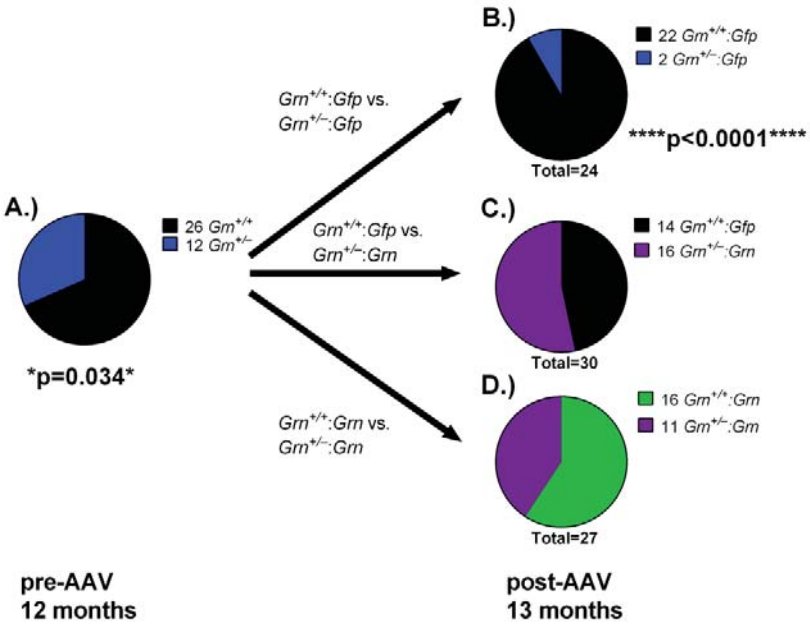

Figure 4: 12 month old $Grn^{+/-}$ mice that exhibited a losing phenotype versus wild-type in the tube test for social dominance (A., p=0.034) had AAV-*Grn* or AAV-*Gfp* infused into the prefrontal cortex and amygdala. After four weeks, AAV-*Gfp*–injected $Grn^{+/-}$ mice still exhibited a losing phenotype versus wild-type (B., p<0.0001). In contrast, AAV-*Grn*–injected $Grn^{+/-}$ mice did not have a significant phenotype versus either wild-type *Gfp*-treated mice (C.) or versus wild-type *Grn*-treated mice (D).

Approach

Aim 1 – To determine if increased mTOR signaling causes abnormal behavior and amygdala dysfunction in progranulin-deficient mice.

Subaim 1 – To investigate the anatomic and temporal association of increased mTOR signaling with abnormal behavior and amygdala dysfunction.

Rationale: Available data from progranulin-deficient model systems point to disruption of mTOR signaling (7, 9, 11). In keeping with these findings, our observation of increased p-S6 (Ser235/236) and p-Akt (Ser473) in the amygdala of $Grn^{+/-}$ mice indicate increased mTOR signaling. Increased mTOR signaling could produce the

abnormal behavior observed in *Grn*$^{+/-}$ mice based on evidence from other mouse models. Increased mTOR signaling disrupts social behavior in the *Tsc1*, *Tsc2*, *Pten*, and *Fmr1* mouse models of autism, and inhibiting mTOR corrects behavioral deficits and neuronal dysfunction in all four lines (47-49). Increased mTOR signaling could also interfere with conditioned fear memory, based on results from S6K1 and S6K2 knockout mice (52, 53). In this aim, we will test our hypothesis that mTOR signaling underlies the abnormal behavior and amygdala dysfunction in progranulin-deficient mice by determining the anatomic and temporal association of increased mTOR signaling with the *Grn*$^{+/-}$ behavioral phenotype.

Approach: We will collect brains for analysis of mTOR signaling from wild-type and *Grn*$^{+/-}$ mice at ages before (3 months), during (5 and 7 months), and after (9 months) the onset of abnormal social behavior. We will use western blot to measure total and phosphorylated levels of several molecules in the mTOR pathway (mTOR (Ser2448), S6 (Ser235/236 and 240/244), S6K1 (Thr389), and Akt (Ser473). These western blots will be performed on brain regions associated with social behavior and conditioned fear (prefrontal cortex and amygdala), as well as a brain region expected to be unaffected (cerebellum). We will also perform immunostaining for these proteins to investigate sub-regions such as central, medial, and basolateral amygdala. Finally, we will perform double-label immunostaining for neuronal (NeuN), astrocytic (GFAP), and microglial (Iba1) markers with the signaling molecule that shows the most dramatic genotype differences. We will image these sections by confocal microscopy to determine which cell type(s) is responsible for the increase in mTOR signaling. All data from these studies will be analyzed by ANOVA with age and genotype as factors using GraphPad Prism 6. Signficant main effects or interactions will be followed by Sidak's post-hoc test to compare wild-type and *Grn*$^{+/-}$ mice at each age.

Predicted Results & Alternative Approaches: Based on our preliminary data, we predict that 7 and 9 month old *Grn*$^{+/-}$ mice will have elevated phosphorylation of mTOR pathway signaling molecules in the cortex and amygdala. The mice may also have elevated phosphorylation of these proteins in the cerebellum, but we would not interpret this as being responsible for the abnormal behavior of *Grn*$^{+/-}$ mice. The 5 month old *Grn*$^{+/-}$ mice should be in the transition to abnormal behavior, and we are unsure of whether to expect significantly increased mTOR signaling. We do not anticipate elevated mTOR signaling in 3 month old *Grn*$^{+/-}$ mice, though we may observe other signaling abnormalities. Reduced p-S6K1 (Thr389) has been reported in 8-10 week old *Grn*$^{-/-}$ mice, so it is possible that altered mTOR signaling could precede abnormal behavior in *Grn*$^{+/-}$ mice (7). Elevated mTOR signaling in 3 month old *Grn*$^{+/-}$ mice would not disprove our hypothesis, but it would complicate the temporal association between elevated mTOR signaling and abnormal behavior. We could then measure signaling in the mTOR pathway in one month old *Grn*$^{+/-}$ mice. These mice would be in the last stages of postnatal development before adulthood, and we would not expect to find any FTD-like characteristics at this age.

The opposite problem could also occur if we fail to observe strong evidence of elevated mTOR signaling in the mice. While we consider this unlikely based on our preliminary data, an alternate strategy would be to investigate MAP kinase signaling. In addition to S6K1 and S6K2 in the mTOR pathway, S6 is phosphorylated by RSK in the MAP kinase pathway (54-57). It is possible that elevated MAP kinase signaling could contribute to the abnormal social behavior and amygdala dysfunction of *Grn*$^{+/-}$ mice, as there is extensive crosstalk between the mTOR and MAP kinase pathways, and increased MAP kinase signaling may also contribute to abnormal social behavior in the *Fmr1* mouse model (48, 58). We could measure the contribution of MAP kinase signaling by measuring phosphorylation of ERK and RSK.

Subaim 2 – *To determine if inhibiting mTOR signaling will prevent or reverse abnormal behavior and amygdala dysfunction in progranulin-deficient mice.*

Rationale: If our hypothesis that progranulin deficiency causes abnormal behavior and amygdala dysfunction by increasing mTOR signaling is correct, then inhibiting mTOR signaling should be able to block the effects of progranulin deficiency on behavior and amygdala function. Administering rapamycin, an inhibitor of the mTORC1 signaling complex, to *Grn*$^{+/-}$ mice is an ideal way to carry out this test (59). Rapamycin is used clinically as an immunosuppressant, but also has beneficial effects in a variety of mouse models of neurodegenerative disease (59, 60). Rapamycin has also been used to normalize social behavior and conditioned fear in autism mouse models (47-49). In this subaim, we will use rapamycin to inhibit mTOR signaling in an attempt to reverse the abnormal behavior of progranulin-deficient mice.

Approach: Rapamycin-supplemented diets are commercially available, and provide an effective way to dose mice with rapamycin without the stress of repeated injections. We will begin by conducting an initial pilot study to determine the dose of rapamycin needed to provide at least a 33% reduction in p-S6 in *Grn*$^{+/-}$ mice. This level of inhibition would be sufficient to bring the *Grn*$^{+/-}$ mice to slightly below wild-type levels. Injections of 5-10 mg/kg of rapamycin per day have been effective at normalizing social behavior in the *Pten*, *Tsc1*, and *Tsc2* mouse models, and provided around 40% reduction in p-S6K in one study (47, 49). We will therefore test diets designed to provide the mice with 5, 10, or 20 mg of rapamycin per kg per day. These diets will be designed using published reports of typical food consumption (61, 62). Group-housed wild-type and *Grn*$^{+/-}$ mice aged 9-12 months will be provided with control or rapamycin-supplemented diets for four weeks before measuring levels of total and phosphorylated S6 by western blot of the cortex and amygdala.

After determining the optimal dose of rapamycin, we will test the ability of rapamycin to prevent or reverse the abnormal behavior and amygdala dysfunction of *Grn*$^{+/-}$ mice by providing control or rapamycin-supplemented diets to *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice for four weeks beginning at ages before (5-6 months) or after (9-12 months) the onset of abnormal behavior. All mice will be pre-screened in the tube test and three-chamber sociability test to confirm presence or absence of a phenotype before beginning rapamycin treatment. Based on results from our laboratory and others, we anticipate that 9-12-month-old *Grn*$^{+/-}$ mice will exhibit abnormal social behavior and elevated mTOR signaling prior to rapamycin administration (1, 27-29). We do not anticipate a behavioral phenotype in the 5-6-month-old mice, though the results from subaim 1 might reveal elevated mTOR signaling at this age. If this is the case, we will use 4 month old mice for the prevention group, and administer rapamycin for 8 weeks. We will group-house the mice unless the pilot study reveals insufficient mTOR inhibition in group-housed mice, as solo-housing can alter social behavior.

After being fed the rapamycin-supplemented diet for four weeks, the mice will undergo testing for social behavior, followed by conditioned fear testing and exposure to a novel, social environment to assess amygdala function. All data from this study except for the tube test will be analyzed by ANOVA with genotype and diet as factors using GraphPad Prism 6. Significant main effects or interactions will be followed by Tukey's post-hoc test for comparison of all experimental groups. Tube test data will be analyzed by the binomial test to compare observed versus expected distributions, with the expected value set at 50% wins for each experimental group.

Predicted Results: If our hypothesis is correct, we predict that inhibiting mTOR signaling with rapamycin will prevent the development of abnormal behavior and amygdala dysfunction in *Grn*$^{+/-}$ mice. Older *Grn*$^{+/-}$ mice do not have neuronal loss, protein aggregation, or other overt signs of neurodegeneration, so we predict that inhibiting mTOR signaling at age 9-12 months will also reverse the behavioral deficits and amygdala dysfunction of these mice. Rapamycin is thought to exert beneficial effects in the brain through a variety of mechanisms such as stimulating autophagy and normalizing both protein synthesis and dendritic spine dynamics, all of which could reverse potential abnormalities in *Grn*$^{+/-}$ mice (47, 48, 60).

Potential Problems and Alternative Approaches: While administering rapamycin through diet avoids the stress of repeated injection, it also introduces the problem of variation in the amount of rapamycin each mouse receives. If variable dosing is a problem in our pilot experiment, we can either solo-house mice with rapamycin-diet or provide rapamycin by daily injection. In this case, we would conduct a second pilot experiment with wild-type mice to determine which method provides the least disruption to social behavior.

Another issue with the proposed studies is the timing of rapamycin administration in the prevention experiment. There is likely some mouse-to-mouse variability in the onset of FTD-like behavior, so it is possible that control *Grn*$^{+/-}$ mice tested at age 6-7 months will not have a significant behavioral phenotype. If this is the case, we will extend the prevention experiment by another four weeks to allow development of a phenotype in control *Grn*$^{+/-}$ mice. This should be possible, as we will test the mice first in the tube test and three-chamber sociability test, which can be repeated.

Aim 2 – To determine if restoring progranulin to progranulin-deficient mice will normalize both mTOR signaling and abnormal behavior.

Rationale: Correcting progranulin deficiency by increasing progranulin levels is the most straightforward approach to treating FTD-*GRN*, but remains untested in an animal model. A key question for the utility of this approach is whether progranulin levels must be increased throughout the brain, or if increasing progranulin

only in FTD-related regions would be sufficient for therapy. We have generated an AAV2/1 vector that expresses mouse progranulin to address these questions, and have obtained promising preliminary data that AAV-*Grn* injected into both the amygdala and prefrontal cortex can reverse the social dominance phenotype of *Grn*$^{+/-}$ mice (Fig.4). With appropriate promoters, AAVs provide high levels of protein expression over long periods of time, making them ideal for this study (Fig.3) (63, 64). In addition to providing the preclinical data for the the utility of this approach for FTD-*GRN*, these experiments will test our hypothesis by determining if correcting progranulin deficiency normalizes mTOR signaling and behavior in *Grn*$^{+/-}$ mice.

Approach: Our preliminary studies indicate that increasing progranulin levels in the prefrontal cortex and amygdala is sufficient to reverse some of the abnormal behavior of *Grn*$^{+/-}$ mice (Fig.4). This is consistent with our previous finding of amygdala dysfunction in *Grn*$^{+/-}$ mice, and the role of the prefrontal cortex in social dominance behavior (1, 65). However, these preliminary data were obtained using an AAV titer (7.36e11 genomes/mL) that produces very high overexpression of progranulin (Fig. 3). We will therefore test an AAV titer that produces less dramatic progranulin overexpression (3.68e10 genomes/mL). We will determine if injection into both the amygdala and prefrontal cortex is sufficient to prevent or reverse abnormal behavior, amygdala dysfunction, and elevated mTOR signaling. After prescreening the mice as described in aim 1, subaim 2, we will perform bilateral infusions of 1 µL of AAV2/1-*Grn* into the basolateral amygdala and prefrontal cortex of *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice at ages before (5-6 months) or after (9-12 months) the onset of abnormal behavior. We will also infuse mice of each genotype with AAV2/1-*Gfp* to serve as controls. Four weeks after AAV infusion, the mice will be tested for behavior, amygdala function, and mTOR signaling as described in aim 1, subaim 2. The mice will undergo tests for social behavior, conditioned fear, and amygdala function. mTOR signaling will be assessed by western blots of amygdala and cortex. Data will be analyzed by ANOVA with genotype and virus as factors, except for the tube test, which will be analyzed by binomial test.

Predicted Results: As described in aim 1, *Grn*$^{+/-}$ mice do not have any neurodegenerative changes that would suggest irreversible damage to the brain. Additionally, our preliminary data supports the ability of AAV-*Grn* to reverse at least some of the behavior deficits of *Grn*$^{+/-}$ mice. We therefore predict that correcting progranulin deficiency at age 9-12 months will normalize mTOR signaling and reverse the behavioral deficits and amygdala dysfunction of *Grn*$^{+/-}$ mice. We also predict that AAV-*Grn* administered at age 5-6 months will prevent these phenotypes from ever developing.

Potential Problems and Alternative Approaches: Our preliminary data makes us confident that we can prevent and reverse the social dominance phenotype of *Grn*$^{+/-}$ mice with AAV-*Grn* injected into the amygdala and prefrontal cortex. However, we may not be able to reverse the entirety of their abnormal behavior with this approach. We do not anticipate this problem for conditioned fear, given the central role of the amygdala in this behavior. However, sociability relies on a wide network of brain regions, and thus may not be normalized by AAV-*Grn* in the amygdala and prefrontal cortex. If this is the case, an alternative approach could be neonatal AAV infusion. Neonatal AAV2/1 infusion into the ventricles produces nearly global infection of the brain, and primarily infects neurons, with minor astrocyte infection, and no detectable microglial infection (66). This approach would also circumvent any problems arising from damage to the amygdala and prefrontal cortex caused by the injection process.

Training Opportunities

My previous training provided me with experience in rodent behavior testing and stereotaxic surgery that will be useful in the proposed studies. However, the experiments proposed in this research plan will require training in several new techniques and approaches. In aim 1, I will investigate abnormalities in a cell signaling pathway (mTOR) to determine molecular/cellular abnormalities in *Grn*$^{+/-}$ mice. I will use confocal microscopy and colocalization in aim 1 to determine the cell type(s) in which mTOR signaling is elevated. In aim 2, I will use an AAV vector to express progranulin in the brain, and will gain experience with the advantages and pitfalls of this approach. These cellular/molecular approaches will complement my current experience with whole animal/functional approaches and provide me with a more complete skill set to pursue a career in neurodegeneration research. Additionally, it is my goal to use data from these experiments as the basis for a K award proposal. If the experiments support the role of mTOR in the abnormal behavior of progranulin-deficient mice, then I expect my future work to focus on the mechanism by which progranulin deficiency disrupts mTOR signaling. This could reveal new aspects of basic progranulin biology with implications not only for neuroscience, but also for diabetes and cancer research.

Vertebrate Animals

1. Proposed Use of Animals

Mouse Strain, Sex, and Age

All mice in the proposed studies will be bred in our animal housing facility. Our progranulin-deficient mouse line has been bred onto a C57Bl6/J background. Our studies require mice at ages both before and after development of abnormal behavior and amygdala dysfunction of *Grn*$^{+/-}$ mice, which occurs around 6-7 months of age. For our time course study of mTOR signaling, we will use mice aged 3, 5, 7, and 9 months. For the prevention and reversal studies with rapamycin or AAV-*Grn*, we will use mice at ages before (5-6 months) and after (9-12 months) the onset of abnormal behavior. In accordance with NIH policy, both male and female mice will be used in these studies. We have not observed a significant sex difference in any outcome measure in prior studies.

Overview of Proposed Studies

In specific aim 1, subaim 1, four groups of mice (aged 3, 5, 7, and 9 months) will be euthanized and brains will be taken for western blotting and immunostaining. In subaim 2 of specific aim 1, we will perform a pilot study in 9-12-month-old *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice to determine the optimal dose of rapamycin to normalize mTOR signaling in *Grn*$^{+/-}$ mice. After determining the appropriate dose, *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice aged either 5-6 months or 9-12 months will be fed a control diet or a diet supplemented with rapamycin for four weeks. They will then undergo behavior testing in the three-chamber sociability test and the tube test for social dominance, and will be tested for conditioned fear. Finally, the mice will be exposed to a novel, social environment and will be euthanized for collection of brains for western blotting and immunostaining. In aim 2, *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice aged 5-6 months or 9-12 months will undergo stereotaxic surgery for infusion of either AAV-*Gfp* or AAV-*Grn* into the brain. After four weeks, the mice will be tested for social behavior and conditioned fear, and will then undergo the novel, social environment protocol described in aim 1.

Description of Behavior Tests

Three-chamber sociability – The three-chamber sociability test involves placing the mouse in a three-chambered box with a small cup in each of the two side chambers. After a 10 minute habituation period, a novel object is placed in one cup, and another mouse is placed in the second cup. (These mice are habituated to placement in the cups for several days prior to testing to minimize distress.) The mouse is then given another 10 minutes to explore the box, and the time spent investigating the novel mouse versus the novel object is used to calculate a social ratio.

Tube Test for Social Dominance – A *Grn*$^{+/+}$ mouse and a *Grn*$^{+/-}$ mouse are placed in opposite ends of a clear, 30.5 cm tube. When released, the mice both try to travel through the tube, and one mouse pushes the other out of the tube. The last mouse remaining in the tube is considered the “winner”.

Conditioned Fear – For conditioned fear testing, mice are placed in a specially-designed conditioned fear box and trained to associate a white noise burst with a 0.5 mA foot-shock. This training session consists of three pairings of 20 s white noise bursts with 2 s, 0.5 mA foot-shocks. The next day the mice are placed back in the box for 5 minutes, and the percentage of the time spent freezing is measured (contextual fear). Later that day the boxes are altered to change the contextual cues, and mouse freezing is measured in response to 3 minutes of the white noise burst used in training (cued fear).

Novel, Social Environment – The purpose of the novel environment protocol is to produce broad neuronal activation that can be used to screen for dysfunctional brain regions. Mice will be switched to solo-housing one week before testing. On the day of testing, *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice will be placed in a cage with a mouse of the opposite sex, but same genotype for two hours prior to euthanasia for collection of the brain. The cage will contain novel objects such as pipette rack lids, a pool of water, and orange slices for the mice to explore.

Animal Numbers

All animal numbers were determined by power analysis of preliminary data using the method described in section 2.

Specific Aim 1, Subaim 1:

Western blotting & Immunostaining: 4 ages x 2 genotypes x (n=14) = **112 mice**

Determined by analysis of the S6 and Akt western blot data shown in figure 2 of the research strategy.

Specific Aim 1, Subaim 2:
Rapamycin dose pilot: 4 doses (0, 5, 10, and 20 mg/kg/day) x 2 genotypes x (n=10) = **80 mice**
Determined by analysis of the S6 western blot data shown in figure 2 of the research strategy.

Rapamycin treatment: 2 ages x 2 diets x 2 genotypes x (n=14) = **112 mice**
Determined by analysis of the behavior and c-Fos data in figure 1 of the research strategy.

Specific Aim 2:
AAV infusion: 2 ages x 2 vectors x 2 genotypes x (n=17) = **136 mice**
Determined by analysis of the behavior and c-Fos data in figure 1 of the research strategy.

Total number of mice: 112 + 80 + 112 + 136 = **440 mice**

2. Justification for Use of Animals

We are using progranulin-deficient mice for these studies because they are the best available model for addressing systems-level questions about FTD with *GRN* mutations. Some molecular questions on the effects of progranulin deficiency have been addressed *in vitro* using primary neurons or neurons derived from induced pluripotent stem cells from FTD patients. However, an animal model is the only way to investigate how molecular changes induced by progranulin deficiency affect outcomes such as behavior or the activity of FTD-related brain regions. The numbers of animals specified above were determined by power analysis with the freely available PS Power and Sample Size Calculations Program (Version 3.0.43, biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) with α set at 0.05 and power set at 0.80. As each study has multiple response variables, the variable with the highest sample size required to achieve a power of 0.8 was used to set the sample size for the experiment. An additional 20% was added to the n for the AAV infusion experiments to account for failed surgeries (injections outside of target regions, mouse death, etc.).

3. Veterinary Care

Mice will be housed in our AALAC approved barrier housing facility with regular veterinary care. All mice are screened for potential health problems during their weekly cage change, and any health cases are addressed by UAB veterinary staff. UAB veterinarians also conduct regular microbiologic screening, necropsy mice that die unexpectedly, and are available for consultation when developing new protocols.

4. Use of Anesthesia and Analgesic Drugs, and Efforts to Minimize Pain and Distress

The only two procedures expected to cause pain and/or distress to the mice are stereotaxic surgery and conditioned fear. Stereotaxic surgeries will be performed under isoflurane anesthesia. According to UAB guidelines, carprofen (5 mg/kg SQ) and buprenorphine (0.1 mg/kg SQ) will be administered prior to making surgical incisions to manage post-surgical pain. Mice will be placed on a heating pad during surgery and for one hour after surgery to maintain body temperature. Conditioned fear training requires presentation of an aversive foot-shock, but the 0.5 mA shocks are not strong enough to injure the mice.

5. Euthanasia

All mice in the proposed studies will be euthanized with a lethal dose of pentobarbital (Fatal Plus, 200 mg/kg pentobarbital IP) followed by transcardial perfusion with 0.9% saline. Full anesthesia will be confirmed by checking for the tail pinch and toe pinch reflexes before beginning perfusions. This method is consistent with AVMA euthanasia guidelines and has been approved by the UAB IACUC.

Data and Resource Sharing Plan

The primary format for data sharing will be publication of the results of the proposed studies. In addition, the primary data will be made available after publication to qualified investigators, through posting on laboratory web sites or distribution in electronic format. Requesting investigators may be asked to defray the costs of distribution if the needs for data are extensive.

The plan for sharing mouse models will adhere to the NIH Policy On Sharing Of Model Organisms For Biomedical Research issued May 7, 2004. (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html). Material Transfer Agreements will be in accord with NIH and University of Alabama policies. Should any intellectual property arise which requires a patent, we would endeavor to ensure that the technology remains widely available to the research community in accordance with the relevant NIH policy documents (http://www.ott.nih.gov/hhs-technology-transfer-policies). Following the characterization and peer-reviewed publication of any transgenic mouse strains generated in this project, mice will be distributed to investigators at academic institutions wanting mice for non-commercial research. Individual requests for shipment of mice generated by this project funding to AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care International) accredited institutions will be honored. The recipient investigators would provide written assurance and evidence that the animals will be used solely in accord with their local IACUC review; that animals will not be further distributed by the recipient without consent; and that animals will not be used for commercial purposes. Requesting investigators may be asked to defray the costs of generating and distributing the animal resources, or transferring them to appropriate repositories. Requests for mice from for-profit corporations to use the mice commercially will be negotiated by our institution's technology transfer office. All licensing shall be subject to distribution pursuant to the University of Alabama's policies and procedures on royalty income. The UAB Technology Transfer Office will report any invention disclosure submitted to them to the appropriate Federal Agency.

Respective Contributions

Dr. Roberson and I contributed to designing the experiments in this proposal, with advice from Dr. Standaert and Dr. Bamman (see letter of support). Dr. Roberson suggested that I investigate S6 kinase signaling based on reports of reduced S6K2 in iPSC-derived neurons from FTD-*GRN* patients (11). After obtaining the preliminary data showing increased p-S6 and p-Akt in $Grn^{+/-}$ mice relative to wild-type, I designed the experiments in aim 1 to investigate mTOR signaling in $Grn^{+/-}$ mice, with advice from Dr. Bamman. Dr. Roberson developed the idea of using an AAV-*Grn* vector to correct progranulin deficiency in aim 2, and I constructed the viral vector. Dr. Standaert provided the AAV backbone used to construct the viral vector. Dr. Standaert also advised me on multiple aspects of the AAV experiment, including choice of serotype and optimizing viral titers. After several discussions with Drs. Roberson, Standaert, and Bamman on the design of the proposed experiments, I wrote the original draft of this research training plan. Dr. Roberson then edited the draft and provided critiques on experimental design that I incorporated into the final training plan. Dr. Standaert and Dr. Bamman also provided helpful feedback on drafts of the research plan. I will conduct all of the proposed experiments and initial statistical analyses. I will meet weekly with Dr. Roberson to discuss results and future experimental plans, and will meet periodically with Dr. Standaert and Dr. Bamman to discuss progress of the research project.

Selection of Sponsors and Institution

I chose Dr. Roberson's laboratory for my postdoctoral training because working in his laboratory provided an opportunity to pursue my research interests while learning new skills on a project directly relevant to human disease. During my graduate training I developed an interest in understanding the neural mechanisms underlying abnormal behavior. Dr. Roberson's work on frontotemporal dementia (FTD) provided an ideal opportunity to achieve this goal. Abnormal behavior is the primary sign of FTD, and arises due to dysfunction of the cortex and amygdala. Understanding the mechanisms behind dysfunction of these brain regions is a major focus of my research in Dr. Roberson's lab, and provides an opportunity to make a significant contribution to the FTD field. The potential for translation of my work is enhanced by Dr. Roberson's membership in the Consortium for Frontotemporal Dementia Research (CFR), a privately funded group of scientists dedicated to developing new FTD therapies.

Dr. Roberson's laboratory also provided an opportunity to acquire valuable new skills. My graduate work provided me with a background in rodent behavior and neurochemical assays such as microdialysis and HPLC. However, I had very little experience with molecular biology and mouse genetics, areas of expertise which are core techniques for modern neuroscience research. This project will provide me with needed experience in cloning, design, and application of gene expression vectors, as well as mouse colony maintenance and breeding. I will also receive training in neurodegeneration through journal clubs and a formal course.

The environment at the University of Alabama at Birmingham was another significant factor in my decision to join the Roberson lab. UAB provides well-equipped labs and animal facilities as well as numerous core facilities. Dr. Roberson has dual appointments in the Depts. of Neurology and Neurobiology, so I have the chance to work with collaborators that are focused on clinical or on basic science. UAB is also committed to postdoc career development through its Office of Postdoctoral Education (OPE). OPE offers multiple career development courses on topics such as grant writing, lab management, job skills, and clinical and translational science.

I chose to invite Dr. David Standaert to be my co-sponsor for this proposal based on his extensive experience with training successful postdoctoral fellows. Dr. Standaert is the chair of Neurology at UAB and brings a wealth of experience in neurodegenerative disorders and gene therapy. Dr. Standaert has trained multiple fellows who have gone on to successful careers in academia and industry, and is well-equipped to guide me as I progress through my training at UAB.

While I have been training in the Roberson lab for around one and a half years, the extra training time requested in this fellowship will be useful due to the length of time needed to complete studies using genetic mouse models. I recently discovered the exciting preliminary data described in this proposal and will require extra time to perform the proposed follow-up experiments. This would allow me to continue to gain technical experience, as well as experience with experimental design, presenting, and writing. Most importantly, the additional training time requested in this fellowship will allow me to generate data for high impact publications and open up new research questions that will be important for furthering my goal of becoming an independent scientist.

Responsible Conduct of Research

I have participated in several responsible conduct of research training events since beginning my postdoctoral fellowship. UAB requires all new postdocs to attend a two-hour RCR seminar that covers issues such as data handling, record keeping, image manipulation, and conflict resolution. This seminar consists of a lecture component as well as break-out discussion sessions. I attended this seminar in April 2013. I attended additional one to two hour seminars in May and August 2013 that covered similar topics and also discussed ethical practices in working with human subjects. I have received additional training in ethical treatment of animal subjects from UAB's Animal Resource Program through several online training modules, and through interaction with UAB staff. In addition to this formal training, Dr. Roberson often incorporates training on ethical research into lab meetings. This includes discussions of data handling, statistics, and imaging.

I plan to continue my RCR training by enrolling in a course offered by UAB on "Principles of Scientific Integrity". This course is taught by Dr. Jeff Engler, UAB's Associate Dean for Academic Affairs and a professor of Biochemistry and Molecular Genetics. Other members of UAB's faculty also contribute to this course. The "Principles of Scientific Integrity" course meets weekly for 2.5 hours for a total of 40 hours of instruction, and covers: examples of past scientific fraud, ideal scientific practices, authorship and peer review, issues associated with the commercialization of research, scientists as public policy advisors, and ethical work with animals and human subjects.

PHS Fellowship Supplemental Form

C. Additional Information

Human Embryonic Stem Cells

1. * Does the proposed project involve human embryonic stem cells? ☐ Yes ☒ No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s):

Fellowship Applicant

2. Alternate Phone Number: 919-491-6575

3. Degree Sought During Proposed Award:

Degree:	If "other", please indicate degree type:	Expected Completion Date (month/year):	
			Reset Entry

4. * Field of Training for Current Proposal: 2890 Neurodegeneration

5. * Current Or Prior Kirschstein-NRSA Support? ☒ Yes ☐ No

If yes, please identify current and prior Kirschstein-NRSA support below:

* Level	* Type	Start Date *(if known)*	End Date *(if known)*	Grant Number *(if known)*	
Postdoctoral	Institutional	02/01/2013	01/31/2015	T32HD71866	Reset Entry
Predoctoral	Individual	05/01/2011	12/31/2012	F31DA032532	Reset Entry
					Reset Entry
					Reset Entry

6. * Applications for Concurrent Support? ☐ Yes ☒ No

If yes, please describe in an attached file: Add Attachment | Delete Attachment | View Attachment

7. * Goals for Fellowship Training and Career: Goals for Training and Career.pd — Add Attachment | Delete Attachment | View Attachment

8. * Activities Planned Under This Award: Activities Planned.pdf — Add Attachment | Delete Attachment | View Attachment

9. Doctoral Dissertation and Other Research Experience: Dissertation and Research Experi — Add Attachment | Delete Attachment | View Attachment

10. * Citizenship:
☒ U.S. Citizen or noncitizen national
☐ Permanent Resident of U.S. Pending
☐ Permanent Resident of U.S.
(If a permanent resident of the U.S., a notarized statement must be provided by the time of award)
☐ Non-U.S. Citizen with temporary U.S. visa

Goals for Fellowship Training and Career

My overall career goal is to run my own laboratory in which I would investigate the neural mechanisms underlying abnormal behavior in animal models, with the goal of translating findings to human patients. I am particularly interested in studying neurodegenerative disorders because they represent a major healthcare challenge of the future with our aging population. Most of these disorders have either no treatments or treatments with limited efficacy, so there is a great need for improved therapies. I feel that as an independent scientist in this field I could make a valuable contribution to the health and well-being of our society.

Becoming an independent scientist in the field of neurodegenerative disorders will require several years of postdoctoral training to build on the foundation provided by my graduate training. My graduate training provided me with a solid background in designing experiments, statistics, and writing fellowship applications and publications. I was also trained in several techniques that will be useful for my future research, including rodent behavior testing, stereotaxic surgery, and immunohistochemistry. However, I still lacked experience with molecular biology, neurodegeneration, and genetic mouse models, including mouse colony maintenance and breeding strategies.

During my postdoctoral training I will be trained in the areas mentioned above, but will also gain experience with other critical scientific skills. I will be continue to be trained in rigorous experimental design and will have the opportunity to write grants, research papers, and a book chapter. I will also obtain experience with running a research program, as I will be the primary researcher overseeing the projects pertaining to frontotemporal dementia with progranulin mutations in the Roberson lab. I have begun training in these areas during the first year of my postdoctoral fellowship, but I still require additional training before I will be ready to develop my own independent project and transition from a postdoc to an independent scientist role. A key goal for my early postdoc years will be obtaining high impact data from which I could build an independent project. To this end, I will spend my fellowship training investigating mTOR signaling in progranulin-deficient mice with the proposed experiments.

In addition to conducting the proposed research, I will participate in coursework to provide additional training in neurodegeneration and to enhance my career development. I will also have the opportunity to supervise and mentor undergraduate and graduate rotation students. This will be a critical skill to develop prior to becoming an independent scientist.

After completion of this proposed fellowship training, I hope to use the skills I've learned and data I've collected to apply for a K99 award during my later postdoc years. This would provide an ideal mechanism to make the final transition from trainee to independent scientist.

Activities Planned Under This Award

Year 1 (2015-2016)

Research: 85% effort

- Aim 1:
  - Western blotting and immunostaining for mTOR pathway signaling molecules
  - Pilot studies to optimize delivery of rapamycin diet
- Aim 2:
  - Begin AAV-*Grn* prevention and reversal experiments

Coursework, Seminars, and Journal Clubs: 12% effort

- Translational Approaches to Neurodegeneration (GBS 729)
- Short course on "Genetics and Genomics in Clinical Research"
- Principles of Scientific Integrity (GRD 717)
- OPE Lab Management Course
- Neurobiology Seminar Series (NBL 703)
- AD/FTD Journal Club (NBL 793)

Scientific Conferences: 2% effort

- Attend and present at Consortium for Frontotemporal Research Discovery Meeting, April, 2015
- Attend and present at McKnight Foundation Inter-Institutional Meeting, April, 2015
- Attend and present at Society for Neuroscience Annual Meeting, November 2015

Other Training Opportunities: 1% effort

- Attend and present at UAB Comprehensive Neuroscience Center Annual Retreat, April, 2015

Year 2 (2016-2017)

Research: 85% effort

- Aim 1:
  - Complete rapamycin prevention and reversal experiments
- Aim 2:
  - Complete AAV-*Grn* experiments
- Write manuscripts on mTOR signaling experiments and AAV-*Grn* experiments

Coursework, Seminars, and Journal Clubs: 2% effort

- Neurobiology Seminar Series (NBL 703)
- AD/FTD Journal Club (NBL 793)

Scientific Conferences: 2% effort

- Attend and present at Consortium for Frontotemporal Research Discovery Meeting, April, 2016
- Attend and present at McKnight Foundation Inter-Institutional Meeting, April, 2016
- Society for Neuroscience Annual Meeting, November 2016

Other Training Opportunities: 1% effort

- Attend and present at UAB Comprehensive Neuroscience Center Annual Retreat, April, 2015

Preparation of K-99 application: 10% effort

Target submission date: October 2016-April 2017

Doctoral Dissertation and Research Experience

My early research interests were in environmental toxicology. During my undergraduate years, I participated in a summer research program in the lab of Dr. Kevin Kleinow at Louisiana State University, in which I helped investigate the estrogenic effects of hydroxyl-polychlorinated biphenyls (OH-PCBs) in zebrafish. I assisted with maintaining the zebrafish colony and dosing the zebrafish with OH-PCBs. I also worked to optimize both the extraction of estradiol from zebrafish tissue and measurement of estradiol levels with an EIA assay. I attended graduate school at Duke University with the intention of continuing environmental toxicology research, but became fascinated with neuroscience while rotating in Dr. Cynthia Kuhn's lab. During my rotation period, I used fast scan cyclic voltammetry to measure the effects of amphetamine on stimulated dopamine release in the striatum of adult and adolescent rats. I observed no age differences in amphetamine's effects, which was consistent with the locomotor effects of low-dose amphetamine. Previous work in the laboratory had shown enhanced locomotor and dopaminergic responses of adolescents to dopamine uptake inhibitors such as cocaine or methylphenidate. The laboratory published this specific sensitivity of adolescents to dopamine uptake inhibitors, and I was listed as a co-author due to my work with amphetamine effects on dopamine release.

After joining Dr. Kuhn's laboratory, I began to investigate how immaturity of the serotonergic system during adolescence alters the adolescent response to drugs and contributes to adolescent-typical behaviors such as increased risk-taking. Adolescent humans and animals exhibit reduced behavioral inhibition, increased risk taking, and lower sensitivity to aversive stimuli that may contribute to increased risk for drug abuse and addiction. Activity of the serotonergic system increases behavioral inhibition, reduces risk taking, and contributes to the aversive effects of drugs of abuse such as cocaine and amphetamine. I therefore hypothesized that immaturity of the serotonergic system in adolescents could contribute to risk taking behavior and increased risk of drug abuse and addiction. I used the light/dark (LD) and elevated plus maze (EPM) tests to investigate behavioral inhibition in adult and adolescent rats. I observed subtle differences in baseline behavior in the LD test that could indicate lower behavioral inhibition in adolescent rats, and observed lower anxiogenic responses to fenfluramine (a serotonin-releasing drug) and fluoxetine (a serotonin uptake inhibitor) in adolescent rats in both tests. This was a potentially important finding as it indicates that the serotonergic system has a reduced ability to inhibit behavior in adolescent rats, supporting the hypothesis of reduced serotonergic behavioral inhibition in adolescents.

I then investigated the mechanism behind these lower behavioral responses by performing microdialysis to assess extracellular serotonin levels in the medial prefrontal cortex. I did not detect a significant difference in baseline extracellular serotonin levels using the zero net flux method of quantitative microdialysis. However, adolescents had a lower response to the serotonin-releasing drug fenfluramine, and to reverse dialysis of potassium chloride to depolarize axons around the probe. These data indicated lower capacity to release serotonin in adolescents and was supported by lower serotonin content measured by HPLC. In contrast, I detected no decrease in the density of serotonergic innervation as measured by immunostaining for the serotonin transporter. These data showed that the reduced anxiogenic response to fenfluramine in adolescent rats was associated with a reduced serotonergic response to fenfluramine. This study formed the basis for my first paper.

I also measured levels of extracellular serotonin following fluoxetine administration in each age group. In contrast to the results with fenfluramine, there was no age difference in the serotonergic response to fluoxetine. This indicated that extracellular serotonin levels do not completely explain the reduced adolescent response to serotonergic drugs. I then turned to post-synaptic mechanisms as a potential contributor to the age differences in drug response. I tested the 5-HT_{1A} receptor agonist 8-OH DPAT and the mixed 5-HT_2 agonist mCPP in the LD test, and found reduced adolescent responses to 8-OH DPAT, but not mCPP, relative to adults. I then investigated the levels of 5-HT_{1A} receptors using ^{3}H-8-OH DPAT binding, but observed no age differences in prefrontal cortex, amygdala, or hippocampus. This lead us to hypothesize that immaturity of 5-HT_{1A}-expressing neural circuits, rather than 5-HT_{1A} receptors themselves, lead to the reduced adolescent behavioral response to 8-OH DPAT. I then tested this hypothesis by measuring the increase in c-Fos immunoreactivity in each age group after a single dose of fluoxetine or 8-OH DPAT, as was used for behavior testing. Adolescent rats had reduced activation of multiple amygdala regions compared to adults after fluoxetine, and reduced activation of the central amygdala and lateral orbital cortex after 8-OH DPAT. These

data suggested that immature amygdala and cortical responses are associated with the reduced behavioral effects of serotonergic drugs in adolescents, and formed the basis for my second paper.

I then published a third paper that used factor analysis to compare LD behavior of adults and adolescents using pooled data from all control animals from the above studies. This study found that LD behaviors load similarly onto anxiety-like and locomotor factors in each age group, suggesting that this test is useful for comparing drug effects between ages. I also included data with the prototypical anxiogenic drugs FG-7142 (a benzodiazepine inverse agonist) and yohimbine (an α_2 adrenergic antagonist) showing reduced responses to these drugs in adolescents. These data, in combination with the above data with serotonergic drugs, suggest that the neural circuits that mediate anxiogenic responses and behavioral inhibition are immature in adolescents.

While nearing completion of my graduate training, I searched for a postdoctoral fellowship that would allow me to continue researching the neural mechanisms of behavior in a way that would contribute to greater understanding of a specific disease. I chose to study a mouse model of frontotemporal dementia (FTD) in Dr. Roberson's lab because this disease involves many of the same behavioral constructs that I became interested in while studying adolescent rats. FTD patients exhibit disinhibited, impulsive behavior and reduced sensitivity to aversive stimuli that is associated with amygdala dysfunction. FTD patients also undergo social withdrawal, reduced empathy, and deterioration of relationships that is likely also due to degeneration of cortical and amygdala regions.

I have completed my first year in Dr. Roberson's lab, and have been studying *Grn*$^{+/-}$ and *Grn*$^{-/-}$ mice as a model of FTD with progranulin mutations. Loss-of–function progranulin mutations are a major cause of FTD, and *Grn*$^{+/-}$ and *Grn*$^{-/-}$ mice are one of the primary mouse models of FTD currently in use. These mice develop abnormal social behavior and fear conditioning deficits by 6-7 months of age, and exhibit reduced activation of the central amygdala when exposed to a novel, social environment. *Grn*$^{-/-}$ mice also develop gliosis, neuro-inflammation, and lipofuscinosis that may model the pathology observed in FTD, as well as neuronal ceroid lipofuscinosis. I have been funded by a T32 grant to determine if exercise can improve the behavioral and histological deficits of progranulin-deficient mice. I have recently completed a study to determine if six weeks of voluntary wheel running could prevent development of behavioral deficits or reduce the inflammation and gliosis of progranulin-deficient mice. I housed *Grn*$^{+/-}$, *Grn*$^{+/-}$, and *Grn*$^{-/-}$ mice in standard cages or cages with running wheels for six weeks and then tested them for abnormal social behaviors and conditioned fear. I then exposed the mice to a novel, social environment and collected brains for c-Fos immunostaining. The behavior data from this study were largely negative, and I observed no effect of exercise on brain progranulin levels. However, *Grn*$^{-/-}$ mice exhibited a modest reduction in neuro-inflammation with exercise. I am currently preparing a manuscript of these data for publication.

In addition to the exercise studies, I have designed an AAV-*Grn* vector and have been working to optimize injection conditions in mice. As described in this proposal, I plan to use AAV-*Grn* to increase progranulin levels in progranulin-deficient mice with the goal of preventing or reversing their FTD-like phenotype. Correcting progranulin deficiency is the most straightforward way to treat FTD with progranulin mutations, and the AAV-progranulin work will provide proof-of–principle that this approach could be useful as a therapeutic strategy. However, targeting downstream pathways of neural dysfunction due to progranulin deficiency may provide more easily druggable targets and could be relevant to FTD without progranulin mutations. Thus, another major aim of my work in Dr. Roberson's lab thus far has been to uncover the mechanism by which progranulin deficiency causes FTD-like behavior. I have recently uncovered the increase in Akt and ribosomal protein S6 phosphorylation that is described in this proposal and think that this could potentially contribute to the FTD-like phenotype of progranulin-deficient mice. I am applying for this fellowship to provide funding for more time to investigate this potentially important finding.

PHS Fellowship Supplemental Form

C. Additional Information (continued)

Institution

11. ☐ Change of Sponsoring Institution

Name of Former Institution:

D. Sponsor(s) and Co-Sponsor(s)

* Sponsor(s) and Co-Sponsor(s) Information: Sponsor Cosponsor Information.pdf [Add Attachment] [Delete Attachment] [View Attachment]

E. Budget

All Fellowship Applicants:

1. * Tuition and Fees:

☐ None Requested ☒ Funds Requested:

Year 1	
Year 2	
Year 3	
Year 4	
Year 5	
Year 6 *(when applicable)*	
Total Funds Requested:	

Senior Fellowship Applicants Only:

2. Present Institutional Base Salary: Amount | Academic Period | Number of Months [Reset Entry]

3. Stipends/Salary During First Year of Proposed Fellowship:

a. Federal Stipend Requested: Amount | Number of Months

b. Supplementation from other sources: Amount | Number of Months

Type (sabbatical leave, salary, etc.)

Source

F. Appendix

[Add Attachments] [Delete Attachments] [View Attachments]

Section II – Sponsor and Co-Sponsor Information

The sponsor for this application is Erik Roberson, MD PhD, Associate Professor of Neurology at UAB. Dr. Roberson is Co-Director of the Center for Neurodegeneration and Experimental Therapeutics at UAB. He trained with Bruce Miller and Lennart Mucke at UCSF/Gladstone and is an expert in mouse models of frontotemporal dementia. He has been at UAB since 2008 and has joint appointments in the Department of Neurobiology, the McKnight Brain Institute, and the Center for Aging at UAB.

The co-sponsor for this application is David G. Standaert, MD PhD, John N. Whitaker Professor and Chair of Neurology at UAB. Dr. Standaert arrived at UAB in 2006 from Massachusetts General Hospital/Harvard Medical School to serve as the first director of the Center for Neurodegeneration and Experimental Therapeutics. Dr. Standaert brings expertise in neurodegenerative disorders, neurochemistry, neuropharmacology, and gene therapy.

Sponsors' Commitment and Role in Training

Sponsor, Dr. Roberson

I am thrilled that Andrew chose to join my lab and am committed to offer him the best possible training environment for his career development. The core elements of our plans are described in this proposal, including executing a rigorous program of hypothesis-driven research on the mechanisms of a deadly neurodegenerative disease as described in the Research Strategy, and completing a thorough program of training in each component necessary for success in research as described in the Training Plan below.

I am fully committed to Andrew's development as a scientist. I meet one-on-one with Andrew every Friday at 9:00 to go over his data from the past week and to set plans for the next one, and will continue to do so throughout the training period. In addition, my office is inside the lab with an open door a few feet from the bench where Andrew works, so he has easy access whenever questions arise.

I believe that trainees benefit from multiple mentors' perspectives, so we invited Dr. David Standaert to serve as a co-mentor for Andrew. Dr. David Standaert is Chairman of the Department of Neurology and directs a basic science laboratory studying mechanisms of Parkinson's disease, as well as numerous clinical trials in movement disorders. We have also asked Dr. Marcas Bamman to advise Andrew on the aspects of his project relating to mTOR signaling. Dr. Bamman is a Professor of Cell, Developmental, and Integrative Biology, and Director of the UAB Center for Exercise Medicine. He is an expert on muscle physiology in response to exercise, particularly the role of mTOR.

Co-sponsor, Dr. Standaert

I am pleased to be able to participate in Andrew's training at UAB. I relocated to UAB from Harvard Medical School in 2006 to build the Center for Neurodegeneration and Experimental Therapeutics (CNET), a new program of translational neuroscience in neurodegeneration to speed the development of novel therapies. Dr. Roberson joined CNET in 2008, has built a thriving research laboratory, and has now taken over leadership of the Center as I became department chair. I think the CNET environment, with state-of-the-art research in the context of close ties to the clinical community, is an excellent one for Andrew's training as he pursues his goal of becoming an independent scientist.

As Chair of the Department of Neurology at UAB, I am committed to training the next generation of physicians and scientists. I have had extensive involvement in this area: I have personally mentored 6 previous and current postgraduate fellows on NIH K awards, three pre-doctoral fellows on NIH F awards, and serve as the PI for the UAB R25 award for training of residents in neurology, neuropathology and neurosurgery. I have also served on a wide range of related NIH review committees, including those for T32, R25, and K awards.

I have worked with Andrew since his arrival at UAB as an advisor for his T32 fellowship. Andrew and I have met approximately once each quarter since his arrival at UAB, and I have aided him in developing and implementing an AAV-progranulin vector in his mouse model. As a co-mentor for Andrew, I will continue to advise him on the technical aspects of his project, and will work with him to ensure that he continues on a productive and successful career development track.

A. Research Support Available

Sponsor, Dr. Roberson

Source	Title	Role	Dates	ADC*
NIH R01-NS075487	Mechanisms for the Benefit of Tau Reduction in Alzheimer Disease Models	PI	7/1/11–6/30/16	
Consortium for FTD Research	Behavioral Abnormalities in Progranulin-deficient Mice	PI	1/1/08–12/31/14	
Alabama Drug Discovery Alliance	Targeting the Tau–Fyn interaction in Alzheimer's Disease	PI	5/1/11–4/30/14	

*ADC, Annual Direct Costs

Co-sponsor, Dr. Standaert

Source	Title	Role	Dates	ADC*
NIH P50NS037406	Molecular Etiology of Early Onset Torsin Dystonia	Project Leader	1/1/00-1/31/15	NCE
Bachmann-Strauss Dystonia and Parkinson Foundation	UAB Bachmann-Straus Dystonia and Parkinson's Disease Center of Excellence	PI	9/15/13-9/14/16	
American Parkinson's Disease Foundation	APDA Advanced Center for Parkinson's Research	PI	9/1/06-8/31/14	
NIH P01NS087997**	Molecular Etiology of Early Onset Dystonia	Project Leader	4/1/15-3/31/20	
Dystonia Medical Research Foundation**	Evaluation of the effects of a novel nicotinic agonist, AZD1446, on neurochemical and electrophysiologic endpoints in DYT1 mouse models	PI	7/1/14-6/30/15	

*ADC, Annual Direct Costs
**Pending support

B. Sponsor's Previous Fellows/Trainees

Sponsor, Dr. Roberson

I established my laboratory at UAB as an Assistant Professor in 2008, and as such, many of my first trainees are still in training. One postdoc (Anthony Filiano) has completed training and is now a Research Scientist at the University of Virginia. Two predoctoral students (Zhiyong Li and Brian Warmus) defended their theses within the last several months. Brian is an MD/PhD student, and is completing his medical training.

Current Trainees, Roberson Lab		
Name	**Period Trained**	**Title**
Alicia Hall	2009–	Graduate Student
Nick Cochran	2011–	Graduate Student
Andrew Arrant	2013–	Postdoctoral Fellow
Travis Rush	2014–	Postdoctoral Fellow

Co-sponsor, Dr. Standaert

Dr. Standaert relocated from Massachusetts General Hospital / Harvard Medical School in 2006. Because of the location and organization of the MGH research laboratories, there are very few predoctoral students involved in MGH research programs. Dr. Standaert has trained 15 previous and two current Postdoctoral trainees; of these five were MD/PhD's, and five were supported by NIH K01 or K08 awards mentored by Dr.

Standaert. Dr. Standaert has three current PhD students; both MD/PhD students are supported by individual NRSA awards.

Representative Trainees, Standaert Lab			
Name	**Period Trained**	**Employing Organization**	**Title or Occupation**
Anthone Dunah, PhD*	1997 – 2000 postdoctoral	Biogen-Idec Inc. Harvard Medical School	Director, Molecular and Cellular Drug Discovery Assistant Professor of Neurology (adjunct)
Nutan Sharma, MD, PhD*	2001– 2006 postdoctoral	Harvard Medical School	Associate Professor of Neurology
Tom Grammatopoulos, PhD	2004–2006 postdoctoral	Link Medicine, Inc	Research Scientist
Talene Yacoubian, MD, PhD*	2005–2007 postdoctoral	UAB	Assistant Professor of Neurology
Travis Lewis*	2007– predoctoral	University of Pennsylvania	Neurology Resident

*NIH K01, K08, or F30 mentored by Dr. Standaert

C. Training Plan, Environment, and Research Facilities

Training Plan. Andrew and I have worked with Dr. Standaert to design a training plan that builds on his previous experience and will provide him with the skills he needs to become a principal investigator in neurodegeneration research. Andrew came to my lab with experience in neurochemistry and neuropharmacology, but requires additional training in cellular signaling, neurodegeneration, disease models, and translational research. Dr. Standaert and I will also work with Andrew to continue to develop his skills in scientific writing, grantsmanship, and experimental design.

Previous Training Experience. As a Toxicology undergraduate student, Andrew completed courses in biology, chemistry, public health, and toxicology. Andrew then pursued his interest in basic science research and earned his PhD in Pharmacology from Duke University, where he was also a member of the Integrated Toxicology and Environmental Health Program. During his graduate training, Andrew completed coursework in basic pharmacology/toxicology and neuroscience, cellular signaling, and statistics. His research training was heavily focused on neurochemistry and neuropharmacology, with very little inclusion of molecular biology or cellular signaling.

Didactic Coursework. Andrew will take the Translational Approaches to Neurodegeneration (GBS 729) course taught by Dr. Andrew West. This course covers the successes and challenges of translational neurodegeneration research by having students participate in discussions, critical debates, and mock study sections.

Andrew will also take a short course on “Genetics and Genomics in Clinical Research” offered by UAB’s Heflin Center for Genomic Sciences. The course consists of five four-hour sessions and is designed to equip researchers to incorporate genomic approaches in their work. The course covers topics such as microarray analysis, gene discovery, analysis of gene methylation, and bioinformatics analysis.

Research Training. To understand the neurobiology of a disease state, I believe one needs to analyze a model organism with a variety of approaches. My mentors impressed on me the importance of being at least fluent (ideally, technically expert) at each level. Andrew came to my lab with experience in behavior testing and stereotaxic surgery, but with very little experience in molecular biology or investigating signaling pathways. Andrew has already gained some molecular biology experience by cloning an AAV-progranulin construct. Working with AAV-progranulin in mice will give him further experience with applying viral vectors in vivo.

Andrew will also gain experience in dissecting out signaling pathway abnormalities through his investigation of mTOR signaling.

Keeping Abreast. To stay abreast of the latest developments in related fields, Andrew will attend:

- Neurobiology Seminar (NBL 703; Thursdays at 1:30). Seminars relate to all aspects of neurobiology, including synaptic physiology and plasticity, learning and memory, development, glial biology, neurobiology of disease, and systems neuroscience. Most of the speakers are from outside institutions.
- Journal Club. Andrew must participate in a formal journal club every semester and will choose between Alzheimer's and Frontotemporal Dementia (GBS 793), Cognition and Cognitive Disorders (NEUR 707), and Neurodegenerative Disease (NBL 787).
- Foundation Meetings. Andrew will attend the annual Consortium for Frontotemporal Dementia Research (CFR) Discovery Meeting. The CFR funds our work on frontotemporal dementia and holds an annual conference at UC San Francisco for trainees to present their findings.
- National Meetings. Andrew will attend at least one national meeting per year, to be selected from the Alzheimer's Association International Conference (AAIC) meeting, the biannual International Conference on FTD, and the Society for Neuroscience (SfN) meeting.

Oral Presentations. Andrew will participate in several forums, ranging in formality, allowing him to develop skills in public speaking and organizing an effective presentation in both poster and platform format.

- Lab Meeting. The Roberson Lab meets weekly for 90 minutes, with each trainee presenting their data at least once every six weeks. We also use lab meetings for practice talks before essentially every outside presentation, and the group provides excellent feedback on both content and delivery.
- Center for Neurodegeneration and Experimental Therapeutics (CNET) Seminars. Members of the core CNET labs, which study a variety of cognitive and movement disorders, meet monthly for a seminar series. Andrew will present a polished 50-min seminar in this forum as his project develops.
- Neurobiology Retreat. The Department of Neurobiology convenes annually for two nights at a lakeside conference center with an outside keynote speaker, 10–15 internal speakers giving 20-min talks, and poster sessions. Andrew will present a poster annually and give a talk at least once.
- National Meetings. I expect Andrew to present annually at the SfN, AAIC, or biannual FTD meeting. Over the course of his. training, he will deliver both poster and platform presentations.

Scientific Writing. The ability to write clearly is one of the most important skills to acquire during scientific training. Andrew will receive both formal and hand-on training in scientific writing.

- I teach a writing course, based on Mimi Zeiger's Essentials of Writing Biomedical Research Papers and complete with homework assignments, for all my trainees. This 18-lesson course is taught after lab meeting, and repeats every other year.
- I expect Andrew to publish multiple original research articles in high-quality, peer-reviewed journals. He is already co-author on a manuscript in preparation.
- Andrew and I will co-author a book chapter on the cerebral cortex in FTD that I was recently invited to write.
- I will periodically offer Andrew the opportunity to assist me in peer-reviewing manuscripts, from which he will learn to accurately, fairly, and confidentially judge others' work and writing.

Grantsmanship and Professional Skills. Andrew's eventual goal is to run his own neurodegeneration research lab. Many skills are necessary for success in that career path, and none are more important than grantsmanship. Writing this proposal is a major aspect of his training in this area, and I will also enlist his help with other applications. I will also encourage him to take the grant writing course offered by UAB's Office of Postdoctoral Education.

Biomedical Ethics. Andrew has attended several seminars on ethics, as detailed in the section on Training in the Responsible Conduct of Research. He will received continuing ethics instruction by taking the Principles of Scientific Integrity course taught by Dr. Jeff Engler, UAB's Associate Dean for Academic Affairs.

Additional Advising. Andrew assembled an advisory committee as part of his T32 training that included Drs. David Standaert and Marcas Bamman. Dr. Standaert is now a co-sponsor of this proposal, and Andrew will

also continue to meet with Dr. Bamman for guidance in his investigation of mTOR signaling (see letter of support). Dr. Bamman is a Professor in the Department of Cell, Developmental, and Integrative Biology, and Director of the UAB Center for Exercise Medicine. Dr. Bamman is an expert on skeletal muscle atrophy, regeneration, and hypertrophy, with extensive experience in studying mTOR signaling. Andrew will meet with Dr. Bamman approximately once per quarter, or more often if needed, to discuss his findings and next steps. Dr. Bamman has also assisted Andrew in selecting appropriate antibodies for mTOR signaling molecules, and has agreed to continue doing so.

Clinical Exposure. I encourage all of my trainees (postdoctoral, graduate, and undergraduate) to periodically attend Memory Disorders and Behavioral Neurology Clinic with me or another neurologist. Firsthand exposure to FTD will be highly motivating for Andrew and contribute significantly to his understanding of the disease.

Research Environment and Facilities

- Comprehensive Neuroscience Center (CNC). With over 240 faculty members, the CNC is the epicenter for Neuroscience on campus. The mission of the CNC is to develop interdisciplinary neuroscience research, clinical care, and education at UAB. The absence of inter-departmental boundaries to collaboration or resource sharing garnered UAB recognition as one of the Scientist magazine's "Best Places to Work in Academia".
- Center for Neurodegeneration and Experimental Therapeutics (CNET). CNET serves as UAB's focal point for translational studies in neurodegenerative diseases, including Alzheimer's, FTD, Parkinson's, ALS, and Huntington's disease. Dr. David Standaert was recruited from Massachusetts General Hospital and Harvard Medical School to serve as the first director of CNET, and Dr. Roberson along with Dr. Andrew West have recently taken over as co-directors now that Dr. Standaert has become department chair. CNET resources include an imaging core facility, which contains instrumentation for conventional light microscopy, confocal microscopy, laser capture microdissection, and computer-assisted unbiased stereology.
- McKnight Brain Institute. The Evelyn F. McKnight Brain Institute for Age-related Memory Loss at UAB focuses its efforts on understanding both memory and memory dysfunction, approaching the problem at all levels from molecular to cognitive. The Institute was founded in 2004 with a gift from the McKnight Brain Research Foundation, which also established a $10 million endowment for the Institute in 2009.
- Office of Postdoctoral Education (OPE). UAB's OPE oversees the university's efforts to enhance the career development of its postdoctoral fellows. OPE works with UAB's postdoctoral association to offer career-enhancing courses and awards to provide funding for conference travel, internships, and extramural courses. The OPE does an excellent job of facilitating postdoctoral training at UAB, resulting in UAB being ranked first among public universities and eigth overall in the most recent survey of "The Best Places to Work for Postdocs" by The Scientist magazine (http://www.the-scientist.com/?articles.view/articleNo/34849/title/Best-Places-to-Work-Postdocs-2013/).

D. Number of Fellows/Trainees to be Supervised During the Fellowship

Sponsor, Dr. Roberson

In addition to Andrew, I am currently training two graduate students and one postdoctoral fellow. I will also serve as a research mentor for several rotation students and undergraduate students doing either independent study or summer research.

Co-sponsor, Dr. Standaert

I am currently training four graduate students and two postdoctoral fellows. I do not anticipate taking on further trainees in my laboratory until one or more of these completes their training.

E. Applicant's Qualifications and Potential for a Research Career

Sponsor, Dr. Roberson

I am thrilled by the opportunity to mentor Andrew, who has every attribute needed to succeed in an academic neuroscience career. He came to my lab with stellar training in behavior and pharmacology, and I think the complementary training in mouse models of neurodegenerative disease that we will provide through this training award will prepare a new star in our field.

Andrew did his undergraduate work at the University of Louisiana at Monroe, graduating summa cum laude with a 4.0 GPA. He enrolled in graduate school at Duke University, where he earned his PhD in Pharmacology with Cynthia Kuhn, working on the role of serotonin in mediating risk-taking behavior. He was very productive as a graduate student, publishing six papers including three as first author. He was awarded an F31 individual NRSA to support his graduate training. Dr. Kuhn referred to him as the most likely to be successful in academia of all the students she had trained in the past 10 years.

Andrew joined my lab a little over a year ago to learn about neurodegenerative disease and mouse models as the next step in preparing himself for a more translational and disease-oriented research career. I suggested that he work on a mouse model of frontotemporal dementia (FTD) that we had begun studying, based on the observation that progranulin haploinsufficiency is one of the most common genetic causes of FTD. A previous postdoc in the lab had found that progranulin haploinsufficient mice develop an interesting and FTD-relevant pattern of abnormalities, with social dysfunction and impaired amygdala function. Andrew has worked on two aspects of the project that come together in this proposal: better defining the molecular mechanisms by which progranulin deficiency impairs neuronal function, and determining whether increasing progranulin will be beneficial for correcting deficits in these mice.

I could not be more impressed by how quickly Andrew has established himself in the lab. He is very technically skilled and quick to master techniques. Even more impressive is how he has taken intellectual ownership of the project and generated fascinating new preliminary data, which forms the basis of this proposal, for a role of mTOR and S6 kinase abnormalities in these mice. Andrew clearly has what it takes to succeed in academics: curiosity, creativity, hard work, the motivation to dig into the literature and the savvy to move a project forward. He combined these talents with a relaxed personality and a willingness to extend himself to help others that has won the respect and admiration of everyone in our Center.

In summary, Andrew has the potential to make major contributions to neurodegeneration research. He has track record of superlative academic success and research productivity, and has generated promising preliminary data in a compelling model of FTD. I urge the review panel to give Andrew its full attention.

Co-sponsor, Dr. Standaert

I believe that Andrew is an excellent candidate for an F32 fellowship, and has the potential to make important contributions in the field of neurodegeneration over the course of his career. Andrew came to UAB with a history of success and productivity in his prior training. He earned graduated with highest honors as a toxicology student at the University of Louisiana at Monroe prior to pursuing a PhD in Pharmacology at Duke University. Andrew's time at Duke was productive, resulting in three first author papers and four co-authorships.

Andrew was recruited to UAB through the T32 in Exercise Medicine led by Dr. Bamman. This is a very successful training program that draws applicants from a national pool. I serve on the steering committee for this T32, and we were very pleased when Andrew agreed to train in the program. He joined the Roberson lab with an interest in performing translational research and the goal of becoming an independent scientist in the field of neurodegeneration. During his time at UAB, Andrew has shown that he has the attributes necessary to achieve this goal, including technical expertise, critical thinking, and attention to detail. This proposal will provide him with further training in cell signaling and translational neurodegeneration research that he will need to achieve independence. The environment of UAB's Center for Neurodegeneration and Experimental Therapeutics and the Roberson lab is exceptionally well-suited to facilitate Andrew's training.

Andrew's proposed research has the potential to provide valuable insight into the molecular mechanisms underlying FTD, and serve as the basis for a career in neurodegeneration research. Andrew has shown the capacity to take advantage of this opportunity and continue his record of productivity. I enthusiastically support Andrew's application and I am committed to helping him to achieve his goals.

OMB Number: 4040-0001
Expiration Date: 6/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. * First Name: Andrew Middle Name:
* Last Name: Arrant Suffix: Ph.D
Position/Title: Postdoctoral Fellow Department: Neurology
Organization Name: University of Alabama at Birmingham Division: School of Medicine
* Street1: 1825 University Blvd, SHEL 1171
Street2:
* City: Birmingham County/ Parish: Jefferson
* State: AL: Alabama Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 352942182
* Phone Number: 205-996-9435 Fax Number: 205-996-9436
* E-Mail: aearrant@uab.edu

Credential, e.g., agency login: arrant

*** Project Role:** PD/PI **Other Project Role Category:**

Degree Type: PhD
Degree Year: 2012

***Attach Biographical Sketch** Arrant Biosketch.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

PROFILE - Senior/Key Person 1

Prefix: Dr. * First Name: Erik Middle Name: D
* Last Name: Roberson Suffix: MD, PhD
Position/Title: Associate Professor Department: Neurology
Organization Name: University of Alabama Birmingham Division: School of Medicine
* Street1: 1825 University Blvd, SHEL 1110
Street2:
* City: Birmingham County/ Parish: Jefferson
* State: AL: Alabama Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 352942182
* Phone Number: 205-996-9486 Fax Number: 205-996-9436
* E-Mail: eroberson@uab.edu

Credential, e.g., agency login: eroberson

*** Project Role:** Other (Specify) **Other Project Role Category:** Sponsor

Degree Type: PhD, MD
Degree Year: 1997, 1999

Attach Biographical Sketch RobersonBiosketchFinal.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

[Delete Entry] [Next Person]

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2

Prefix: Dr. * First Name: David Middle Name: G

* Last Name: Standaert Suffix: MD, PhD

Position/Title: Professor/Chairman Department: Neurology

Organization Name: University of Alabama Birmingham Division: School of Medicine

* Street1: 1719 7th Ave. S.,CIRC 516

Street2:

* City: Birmingham County/ Parish: Jefferson

* State: AL: Alabama Province:

* Country: USA: UNITED STATES * Zip / Postal Code: 352940017

* Phone Number: 205-996-6329 Fax Number: 205-996-6580

* E-Mail: dstandaert@uab.edu

Credential, e.g., agency login:

*** Project Role:** Other (Specify) **Other Project Role Category:** Sponsor

Degree Type: PhD, MD

Degree Year: 1988, 1988

Attach Biographical Sketch	Standaert Biosketch.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

Delete Entry Next Person

To ensure proper performance of this form; after adding 20 additional Senior/ Key Persons; please save your application, close the Adobe Reader, and reopen it.

FELLOWSHIP APPLICANT BIOGRAPHICAL SKETCH

USE ONLY FOR INDIVIDUAL PREDOCTORAL and POSTDOCTORAL FELLOWSHIPS. DO NOT EXCEED FOUR PAGES.

NAME OF FELLOWSHIP APPLICANT	POSITION TITLE
Andrew Arrant	Postdoctoral Trainee
eRA COMMONS USER NAME (credential, e.g., agency login) ARRANT	

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Louisiana at Monroe, Monroe, LA	B.S.	05/2007	Toxicology
Duke University, Durham, NC	Ph.D.	12/2012	Toxicology/Pharmacology
University of Alabama at Birmingham (postdoc) Birmingham, AL	n/a	n/a	Neurology

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

The goal of this proposal is to investigate the mechanism by which progranulin deficiency causes neuronal dysfunction and FTD-like behavior in *Grn*$^{+/-}$ mice, and to reverse these deficits by targeting either the mTOR signaling pathway or progranulin deficiency itself. I am excited about conducting the experiments in this proposal because I think they can provide a foundation for a career as an independent scientist by giving me training in new areas, leading to multiple publications, and opening up new avenues of research into the interaction of progranulin and mTOR signaling. My time in Dr. Roberson's laboratory so far has been an excellent training experience, as I have gained experience in molecular biology, cell culture, and cloning through developing and testing an AAV vector. During the proposed fellowship period, I will receive additional training in neurodegeneration, molecular biology, cellular signaling, and mouse genetics by conducting research and attending journal clubs and courses. The proposed research training plan will also allow me to build on the training in rodent behavior testing and stereotaxic surgery that I received during graduate school. My graduate training focused on how development of the serotonergic system during adolescence alters the response to drugs and contributes to adolescent-typical behaviors that could increase risk for addiction, such as risk taking and disinhibition. This experience provided me with training in pharmacology and toxicology, and lead to three first-author publications. During the course of this work, I developed an interest in investigating the neural mechanisms of behavior. I was particularly interested in finding a postdoctoral position that would allow me to pursue this interest in the context of a particular disease, as I am motivated by the prospect that my work could one day be beneficial to patients. I found such a position in Dr. Erik Roberson's laboratory with an opportunity to investigate how progranulin deficiency leads to FTD-like behavior in progranulin-deficient mice. FTD is a devastating disease that primarily manifests as altered behavior, and has no disease modifying therapies. The mechanisms underlying abnormal behavior in FTD are unknown, aside from the brain regions affected by the disease. Our work with progranulin-deficient mice could help address the need for a better understanding of the mechanisms and potential treatments for FTD. This exciting translational aspect of the project will be facilitated by Dr. Roberson's membership in the Consortium for Frontotemporal Dementia Research (CFR), an organization composed of scientists from multiple institutions that is dedicated to developing treatments for FTD. One of my career goals is to start my own lab, in which I could investigate mechanisms of abnormal behavior with the goal of translating these findings to patients. If our hypothesis is correct, the proposed experiments could provide a foundation on which to start a lab by opening the question of how progranulin interacts with mTOR signaling.

B. Positions and Honors

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
Summer Intern	06/05	08/05	Environmental Science	Louisiana Dept. of Environmental Quality	Kirk Cormier
Summer Research Student	06/06	08/06	Environmental Toxicology	Louisiana Biomedical Research Network/Louisiana State University	Kevin Kleinow
Postdoctoral Fellow	01/13	present	Neurology	University of Alabama at Birmingham	Erik Roberson

Academic and Professional Honors
B.S. awarded summa cum laude, University of Louisiana at Monroe, 2007

C. Publications

Research Papers:

Walker, Q.D., Morris, S.E., **Arrant, A.E.**, Nagel, J.M., Parylak, S., Zhou, G., Caster, J.M., and Kuhn, C.M. 2010. Dopamine uptake inhibitors but not dopamine releasers induce greater increases in motor behavior and extracellular dopamine in adolescent than adult male rats. J Pharmacol Exp Ther 335, 124-132. PMCID: PMC2957786.

Walker, Q.D., Johnson, M.L., Van Swearingen, A.E., **Arrant, A.E.**, Caster, J.M., and Kuhn, C.M. 2012. Individual differences in psychostimulant responses of female rats are associated with ovarian hormones and dopamine neuroanatomy. Neuropharmacology 62, 2267-2277. PMCID: PMC3516200.

Biskup, C.S., Sanchez, C.L., **Arrant A.**, Van Swearingen, A.E., Kuhn, C., and Zepf, F.D. 2012. Effects of acute tryptophan depletion on brain serotonin function and concentrations of dopamine and norepinephrine in C57Bl/6J and BALB/cJ mice. PloS One 7, e35916. PMCID: PMC3357407.

Arrant, A.E., Jemal, H., and Kuhn, C.M. 2013. Adolescent male rats are less sensitive than adults to the anxiogenic and serotonin-releasing effects of fenfluramine. Neuropharmacology 65, 213-222. PMCID: PMC3521096.

Arrant, A.E., Schramm-Sapyta, N.L., and Kuhn, C.M. 2013. Use of the light/dark test for anxiety in adolescent and adult male rats. Behav Brain Res 256, 119-127. PMC Journal – In Process.

Arrant, A.E., Coburn, E., Jacobsen, J., and Kuhn, C.M. 2013. Lower anxiogenic effects of serotonin agonists are associated with lower activation of amygdala and lateral orbital cortex in adolescent male rats. Neuropharmacology 73, 359-367. PMCID: PMC3812685.

Sanchez, C.L., Van Swearingen, A.E., **Arrant, A.E.**, Kuhn, C.M., and Zepf, F.D. 2014. Dietary manipulation of serotonergic and dopaminergic function in C57Bl/6J mice with amino acid depletion mixtures. J Neural Transm 121, 153-162. PMC Journal – In Process.

Ward, M.E., Taubes, A., Chen R., Miller, B.L., Sephton, C.F., Gelfand, J.M., Boscardin, J., Minami, S.S., Herl-Martens, L., Seeley, W.W., Yu, G., Herz, J., Filiano, A.J., **Arrant, A.E.**, Roberson, E., Kraft, T.W., Farese, R.V., and Green, A. 2014. Early retinal neurodegeneration and impaired Ran-mediated nuclear import of TDP-43 in progranulin-deficient FTLD. J. Exp. Med. Accepted for publication.

Arrant, A.E.*, Filiano, A.J.*, Young, A.H., Martens, L.H., Farese Jr., R.V., and Roberson, E.D. 2014. Selective Progranulin Deficiency in Neurons Produces Frontotemporal Dementia-Like Deficits. In preparation. * = co-first authors

Arrant, A.E., Patel, A.R., and Roberson, E.D. The Effects of Exercise on Progranulin Levels and Inflammation in Progranulin-Deficient Mice. In preparation.

Abstracts:

Arrant, A.E., Walker, Q.D., and Kuhn, C.M. 2008. The effects of amphetamine on electrically stimulated dopamine release in the striatum of adult and adolescent rats. Abstract for poster presentation, Society for Neuroscience Annual Meeting, Washington D.C.

Arrant, A.E. and Kuhn, C.M. 2009. Divergent effects of serotonin depletion on anxiety in adult and adolescent rats. Abstract for poster presentation, Society for Neuroscience Annual Meeting, Chicago, IL.

Arrant, A.E., Jemal, H., and Kuhn, C.M. 2010. Adolescent rats are less sensitive to the anxiogenic and serotonin releasing effects of fenfluramine. Abstract for poster presentation, Society for Neuroscience Annual Meeting, San Diego, CA.

Arrant, A.E. and Kuhn, C.M. 2011. Dissociation of the anxiogenic and serotonergic effects of acute fluoxetine treatment in adolescent rats. Abstract for poster presentation, Society for Neuroscience Annual Meeting, Washington, D.C.

Arrant, A.E. and Kuhn, C.M. 2012. Immature serotonergic regulation of anxiety-like behavior in adolescent male rats. Abstract for poster presentation, Experimental Biology Meeting, San Diego, CA

Arrant, A.E. and Kuhn, C.M. 2012. Reduced 5-HT_{1A} regulation of anxiety-like behavior in adolescent male rats. Abstract for poster presentation, Society for Neuroscience Annual Meeting, New Orleans, LA

Arrant, A.E., Filiano, A.J., Young, A.H., and Roberson, E.D. Selective progranulin deficiency in neurons produces frontotemporal dementia-like deficits, Abstract accepted for poster presentation, Society for Neuroscience Annual Meeting, Washington, D.C.

D. Scholastic Performance

YEAR	SCIENCE COURSE TITLE	GRADE
	UL Monroe	
2003	Principles of Biology I	
2003	General Chemistry I	
2004	General Chemistry II	
2004	Introduction to Psychology	
2004	Human Physiology I	
2004	Organic Chemistry I	
2005	Human Physiology II	
2005	Organic Chemistry II	
2005	Biochemistry I	
2006	Clinical Chemistry and Toxicology	
2006	Pharmacology	
2006	Public Health Science	
	Duke University	
2007	Essentials of Pharmacology/Toxicology	
2008	Interdisciplinary Approach to Pharmacology II	

YEAR	OTHER COURSE TITLE	GRADE
	UL Monroe	
2006	Technical Writing for Health Sciences	
	Duke University	
2010	Intro to College Teaching	N/A
2010	Statistics for Basic Biomedical Science	
	UAB	
2013	Translational Medicine Course for M.D. and Ph.D. Postdoctoral Scholars	N/A

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
2009	Interdisciplinary Approach to Pharmacology				
2009	Cellular Signaling				
2010	Concepts in Neuroscience I				

GRE Scores (Taken September 2006)
Verbal:
Quantitative:
Analytical Writing:

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Erik D. Roberson	Associate Professor of Neurology Virginia B. Spencer Professor of Neuroscience
eRA COMMONS USER NAME eroberson	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Princeton University, Princeton, NJ	A.B.	1990	Molecular Biology
Baylor College of Medicine, Houston, TX	Ph.D.	1997	Neuroscience
	M.D.	1999	Medicine
	Internship	1999–2000	
University of California, San Francisco (UCSF)	Residency	2000–2003	Neurology
	Fellowship	2003–2005	Behavioral Neurology
Gladstone Institute of Neurological Disease	Fellowship	2003–2006	Neurodegenerative Disease

A. Personal Statement

My career is devoted to understanding mechanisms of cognitive and behavioral impairment in Alzheimer's disease (AD) and frontotemporal dementia (FTD) and to discovering and delivering better therapies for these devastating neurodegenerative diseases. As a physician-scientist, I divide my time between laboratory research, clinical research, and clinical care. My laboratory uses mouse models to study the neurobiological basis of neuronal dysfunction in these disorders. The microtubule-associated protein tau is a common theme and area of focus and we also work on mechanisms related to Aβ and progranulin. I am also a PI for clinical trials in AD and other tauopathies and see patients with AD and other dementias in a weekly outpatient memory disorders clinic. I am committed to training the next generation of researchers, and am excited to mentor Andrew in his investigation of progranulin-deficient mice. Andrew is leading my laboratory's effort to use progranulin-deficient mice to gain insight into the molecular mechanisms underlying FTD with progranulin (*GRN)* mutations. I will ensure that Andrew gains new skills in molecular biology and mouse genetics through his work, and will foster his development of other critical skills such as scientific writing, presenting, and grantsmanship.

B. Positions and Honors

Positions

1990–1999	MD/PhD Student, including graduate work (1991-97) with Dr. David Sweatt, Division of Neuroscience, Baylor College of Medicine, Houston, TX
1999–2000	Intern, Baylor College of Medicine
2000–2003	Resident & Chief Resident in Neurology, UCSF
2003–2005	Clinical Fellow in Behavioral Neurology with Dr. Bruce Miller, UCSF
2003–2006	Research Scientist with Dr. Lennart Mucke, Gladstone Institute of Neurological Disease
2005–2008	Assistant Adjunct Professor of Neurology, UCSF
2006–2008	Staff Scientist, Gladstone Institute of Neurological Disease
2008–2012	Assistant Professor of Neurology and Neurobiology, UAB
2012–	Associate Professor of Neurology and Neurobiology with tenure, UAB

Honors

1990	Highest Honors — Princeton University
1990	Phi Beta Kappa
1990–1999	Presidential Scholar — Baylor College of Medicine Executive Faculty
1992–97	Life and Health Insurance Medical Research Fund Young Scientist M.D./Ph.D. Scholar
1999	High Honors — Baylor College of Medicine
1999	Alpha Omega Alpha
2002–2003	Chief Resident in Neurology — UCSF
2004	Giannini Family Foundation Fellow

2004	S.D. Bechtel, Jr., Young Investigator Award
2005	Kathryn Grupe Award for Excellence in Alzheimer's Disease Research
2012	McNulty Civitan Scientist Award
2013–	Virginia B. Spencer Endowed Professor of Neuroscience

C. Publications (selected from a total of 55)

1. **Roberson, E.D.**, and J.D. Sweatt. (1999). A biochemical blueprint for long-term memory. *Learn. Mem*. 6:381–388.
2. **Roberson, E.D.**, J.H. Hesse, K.R. Rose, H. Slama, K. Yaffe, M.S. Forman, C.A. Miller, J.Q. Trojanowski, J.H. Kramer, and B.L. Miller. (2005). Frontotemporal dementia progresses to death faster than Alzheimer's disease. *Neurology* 65:719–725.
3. **Roberson, E.D.,** and L. Mucke. (2006). 100 years and counting: Prospects for defeating Alzheimer's disease. *Science*. 314:781–784.
4. Mueller-Steiner, S., Y. Zhou, H. Arai, **E.D. Roberson**, B. Sun, J. Chen, X. Wang, G.-Q. Yu, L. Esposito, L. Mucke, and L. Gan. (2006). Anti-amyloidogenic and neuroprotective functions of cathepsin B: implications for Alzheimer's disease. *Neuron* 51:703–714.
5. **Roberson, E.D.**, K. Scearce-Levie, J.J. Palop, F. Yan, I. Cheng, T. Wu, H. Gerstein, G.-Q. Yu, and L. Mucke. (2007). Reducing endogenous tau ameliorates Aβ-induced deficits in an Alzheimer's disease mouse model. *Science*, 316:750–754.
6. Palop, J.J., J. Chin, **E.D. Roberson**, J. Wang, M. Thwin, N. Bien-Ly, J. Yoo, G.-Q. Yu, A. Kreitzer, S. Finkbeiner, J.L. Noebels, and L. Mucke. (2007). Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron*, 55:697–711.
7. **Roberson, E.D.**, B. Halabisky, J.W. Yoo, J. Yao, J. Chin, F. Yan, T. Wu, P. Hamto, N. Devidze, G.-Q. Yu, J.J. Palop, J.L. Noebels, and L. Mucke. (2011). Amyloid-β/Fyn–induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. *J. Neurosci.*, 31:700–711. [PMCID: PMC3325794]
8. **Roberson, E.D.**, O.A. Hope, R.C. Martin, and D. Schmidt. (2011). Geriatric epilepsy: research and clinical directions for the future. *Epilepsy Behav*., 22:103–111.
9. Hall, A.M, and **E.D. Roberson**. (2012). Mouse models of Alzheimer's disease. *Brain Res. Bull*., 88:3–12. [PMCID: PMC3546481]
10. Jin, Y., P.-C. Chen, J.A. Watson, B.J. Walters, S.E. Philips, K. Green, R. Schmidt, J.A. Wilson, G.V. Johnson, **E.D. Roberson**, L.E. Dobrunz, and S.M. Wilson. (2012). Usp14 deficiency increases tau phosphorylation without altering tau degradation or causing tau-dependent deficits. *PLoS ONE*, 7:e47884. [PMCID: PMC3683306]
11. **E.D. Roberson**. (2012). Mouse models of frontotemporal dementia. *Ann. Neurol*., 72:837. [PMCID: PMC3539234]
12. Filiano, A.J., L.H. Martens, A.H. Young, B.A. Warmus, P. Zhou, G. Diaz-Ramirez, J. Jiao, Z. Zhang, E.J. Huang, F.-B. Gao, R.V. Farese, Jr., and **E.D. Roberson**. (2013). Dissociation of frontotemporal dementia–related deficits and neuroinflammation in progranulin haploinsufficient mice. *J. Neurosci.,* 33:5352–5361. [PMCID: PMC3740510]
13. Seward, M.E., E. Swanson, A. Norambuena, A. Reimann, J.N. Cochran, R. Li, **E.D. Roberson**, and G.S. Bloom. (2013). Amyloid-β signals through tau to drive ectopic neuronal cell cycle re-entry in Alzheimer's disease. *J. Cell. Sci*., 126:1278–1286. [PMCID: PMC3635465]
14. Cochran, J.N., A.M. Hall, and **E.D. Roberson**. (2014) The dendritic hypothesis for Alzheimer's disease pathogenesis. *Brain Res. Bull.,* doi: 10.1016/j.brainresbull.2013.12.004. [PMCID: PMC3989444]

15. Qiu, H., S. Lee, Y. Shang, W.-Y. Wang, K.F. Au, S. Kamiya, S.J. Barmada, S. Finkbeiner, H. Lui, C.E.Carlton, A.A. Tang, M.C. Oldham, H. Wang, J. Shorter, A.J. Filiano, **E.D. Roberson**, W.G. Tourtellotte, B. Chen, L.-H. Tsai, and E.J. Huang. (2014.) ALS-associated mutation FUS-R521C causes DNA damage and RNA splicing defects. *J. Clin. Invest.*, doi: 10.1172/JCI72723. [PMCID: PMC3938263]

D. Research Support

Ongoing Research Support

R01 NS075487 Roberson (PI) 7/1/11–6/30/16
NIH/NINDS
"Mechanisms for the Benefit of Tau Reduction in Alzheimer Disease Models"
The major goal of this project is to determine when and in which cell types tau reduction is effective for preventing Aβ-induced neuronal dysfunction.
Role: PI

R01 AG021927 Marson (PI) 4/1/03–6/30/15
NIH/NIA
"Functional change in mild cognitive impairment"
The major goal of this project is to examine neuroanatomic correlates of declining financial capacity in subjects with mild cognitive impairment.
Role: Investigator

R21 AG042716 Wang (PI) 8/1/12–7/31/14
NIH/NIA
"Preclinical test for the efficacy of adrenergic agents in treatment of AD"
The major goal of this project is to determine if adrenergic modulation affects outcome in mouse models of Alzheimer's disease.
Role: Investigator

N/A Roberson (PI) 1/1/13–12/31/14
Consortium for Frontotemporal Dementia Research
"Progranulin mouse models of frontotemporal dementia"
The major goal of this project is to examine behavioral phenotypes in mouse models of progranulin deficiency–related FTD.
Role: PI

N/A Roberson (PI) 5/1/11–4/30/15
Alabama Drug Discovery Alliance
"Targeting the Tau–Fyn interaction in Alzheimer's Disease"
The major goal of this project is to identify inhibitors of Tau–Fyn interactions.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
David George Standaert	John N. Whitaker Professor and Chair of Neurology
eRA COMMONS USER NAME (credential, e.g., agency login) dgstandaert	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	1982	Biochemistry
Washington University, St. Louis, MO	M.D., Ph.D.	1988	Medicine, Pharmacology
Jewish Hospital, St. Louis, MO	Intern	1988-1989	Internal Medicine
University of Pennsylvania, Philadelphia, PA	Resident	1989-1992	Neurology
Massachusetts General Hospital	Fellow	1992-1995	Movement Disorders

A. Personal Statement

Dr. Standaert is a physician-scientist with a long-standing interest in the basic and clinical aspects of neurodegenerative diseases. Dr. Standaert has a substantial track record of mentoring neuroscientists. He has trained more than 20 postdoctoral fellows, which include both basic and clinical scientists, and has served as primary mentor for a total of 6 NIH K awards. He has mentored 2 previous graduate students, one of which was supported by an F30 award. He is currently mentoring 4 graduate students, two of which are supported by F31s. He also has served as co-mentor for 1 past and 1 current graduate student (current student supported by F31). He has served on NIH study sections responsible for review of T32, R25, and F30/31 applications. Additionally, Dr. Standaert is the Program Director of an R25 program for residents in Neurology, Neurosurgery, and Neuropathology.

Dr. Standaert has worked with Dr. Arrant and Dr. Roberson on the development of this project. He will serve as co-mentor for this project, and will participate in both the scientific and the career development aspects of the training program. Relevant to this application, he has substantial expertise in neurodegenerative disorders, neurochemistry/neuropharmacology, and gene therapy. The Whitaker Endowed Chair supports a substantial part of Dr. Standaert's effort and allows for the flexible time allocation required to participate as mentor, and his role as Chair of the Department of Neurology will ensure the access to resources required to successfully complete the research and training programs.

B. Positions and Honors

1982	Graduated magna cum laude from Harvard University
1988	Irwin Levy Prize in Neurology and Neurological Surgery
1991	Sam Zeritsky Resident's Research Award in Neurology
1992-1995	Research and Clinical Fellow, Neurology Service, Massachusetts General Hospital, Boston, MA
1992-1995	American Academy of Neurology Research Fellowship Award in Neuropharmacology
1992-1995	Howard Hughes Medical Institute Postdoctoral Research Fellowship for Physicians
1995-2001	Assistant Professor of Neurology, Harvard Medical School, Boston, MA
1996-1999	Cotzias Fellowship, American Parkinson's Disease Association
2001-2006	Associate Professor of Neurology, Harvard Medical School, Boston, MA
2003-2008	Scientific Advisory Board, Dystonia Medical Research Foundation
2003-2008	Chairperson, Standards Committee, Parkinson Study Group
2004-2006	Associate Director, Movement Disorders Unit, Massachusetts General Hospital
2004-2008	Initial Review Group NSD-B, National Institutes of Health, regular member
2005-2006	Chair, Partners Human Research Committee (IRB), MGH Panel A
2005-2006	Director, MGH/MIT Morris Udall Center of Excellence in PD Research
2006	Chair, ZNS1, NIH Udall Centers Review Panel
2008-2011	Director, Comprehensive Neuroscience Center, UAB
2001-present	Scientific Advisory Board, American Parkinson Disease Association
2005-present	Scientific Advisory Board, Michael J. Fox Foundation

2005-present Handling Editor, Journal of Neurochemistry
2006-present Professor of Neurology, Neurobiology, Cell, Developmental and Integrative Biology, and Pharmacology and Toxicology, University of Alabama at Birmingham (UAB)
2006-2013 Director, Center for Neurodegeneration and Experimental Therapeutics, UAB
2006-present Director, Division of Movement Disorders, Dept of Neurology (UAB)
2007-present "Best Doctors in America"
2008-present Fellow, American Academy of Neurology
2011-present Editorial Board, *Movement Disorders*
2011-present Chair, Department of Neurology, UAB
2013-present Chair, Scientific Advisory Board, American Parkinson Disease Association

C. Selected Peer-reviewed Publications (15 selected from >160)

1. Hoglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, Rademakers R, de Silva R, Litvan I, Riley DE, van Swieten JC, Heutink P, Wszolek ZK, Uitti RJ, Vandrovcova J, Hurtig HI, Gross RG, Maetzler W, Goldwurm S, Tolosa E, Borroni B, Pastor P, Cantwell LB, Han MR, Dillman A, van der Brug MP, Gibbs JR, Cookson MR, Hernandez DG, Singleton AB, Farrer MJ, Yu CE, Golbe LI, Revesz T, Hardy J, Lees AJ, Devlin B, Hakonarson H, Muller U, Schellenberg GD. (2011) Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. *Nat Genet*. 43 (7):699-705. **PMCID**: PMC3125476.
2. Amara AW, Standaert DG, Guthrie S, Cutter G, Watts RL, Walker HC. (2012) Unilateral subthalamic nucleus deep brain stimulation improves sleep quality in Parkinson's disease. *Parkinsonism Relat Disord*. 18 (1):63-68. **PMCID**: PMC3249526.
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D. Research Support

ONGOING

1R25NS079188, Standaert (PI) 4/1/12 – 3/31/17
NIH/NINDS
UAB Research and Education Program in Neurology, Neurosurgery, and Neuropathology

2P50NS037409-12, Standaert (Project PI), Breakefield (Center Director) 1/1/00 – 7/31/14
NIH/NINDS
Program Project: Molecular Etiology of Early Onset Torsin Dystonia
Role: Principal Investigator (Project 1)

APDA, Standaert (PI) 9/1/06 – 8/31/14
American Parkinson's Disease Association
APDA Advanced Center for Parkinson's Research

MJFF Target Validation 2013, Standaert (PI) 1/15/14 – 1/14/16
The Michael J. Fox Foundation for Parkinson's Disease Research
Validation of the Class II MHC Transactivator (CIITA) in Models of PD

RJG Foundation Research Grant, Standaert and Harms (Co-PIs) 12/01/11 – 11/30/14
RJG Foundation
Role of MHC II proteins in Parkinson's-related inflammation
Role: Co-PI

U10NS044547, Standaert (PI) 1/1/13 – 11/30/15
NIH/NINDS
PD Neuroprotection Clinical Trial Center

PPMI, Standaert (PI) 7/27/10 – 7/26/15
Michael J. Fox Foundation
The Parkinson Progression Markers Initiative (PPMI)

Bachmann-Strauss, Standaert (PI) 5/1/13 – 4/30/16
The Bachmann-Strauss Dystonia & Parkinson Foundation, Inc
UAB Bachmann-Straus Dystonia and Parkinson's Disease Center of Excellence

M12-920, Standaert (PI) 12/20/12-12/19/17
AbbieVie Laboratories
An Open-Label, Two Part, Multicenter Study to Assess the Safety and Efficacy of Levodopa-Carbidopa Intestinal Gel (LCIG) for the Treatment of Non-Motor Symptoms in Subjects with Advanced Parkinson's Disease

CERE 120-09, Standaert (PI) 06/13/13 – 06/02/15
CEREGENE, INC

A Phase 1/2 Trial Assessing the Safety and Efficacy of Bilateral Intraputaminal and Intranigral Administration of CERE-120 (Adeno-Associated Virus Serotype 2[AAV2]-Neurturin{NTN]) in Subjects with Idiopathic Parkinson's Disease (CERE 120-09)

1R01NS064934, West (PI) 9/1/10 – 8/31/15
NIH/NINDS
Mechanisms of LRRK2 Mediated Neurotoxicity
Role: Investigator

1U18NS082132-01, West (PI) 09/30/12 – 06/30/15
NIH/NINDS
LRRK2 and Other Novel Exosome Proteins in Parkinson's Disease
Role: Co-Investigator

CA-1059-A-13, Benveniste (PI) 11/1/09 – 10/31/14
National Multiple Sclerosis Society
Collaborative MS Research Center Award
Role: Co-Investigator

K01NS069614 Gray (PI) 4/1/10 – 3/31/15
NIH/NINDS
The Role of Astrocytes in Huntington's Disease
Role: Mentor

K23NS080912, Amara (PI) 09/26/12 – 07/31/17
NIH/NINDS
The Effect of Low Frequency STN DBS on Sleep and Vigilance in PD Patients
Role: Mentor

F31NS076017, Allen (PI) 9/1/11 – 8/31/14
NIH/NINDS
Role of complement in alpha-synuclein based models of Parkinson disease
Role: Sponsor

F31NS081963, Moehle (PI) 9/28/12 – 9/27/15
NIH/NINDS
Role of Microglial LRRK2 in Inflammation
Role: Co-Sponsor

1F31NS084722, Thome (PI) 4/1/14 – 3/31/16
NIH/NINDS
Role of microRNAs in modulating inflammation in alpha-syn mediated models of PD
Role: Sponsor

COMPLETED (Selected, Last Five Years)

MJFF Therapeutics Development Program, Standaert (PI) 9/1/08 – 1/30/10
Michael J. Fox Foundation
Validation of TorsinA as a Target for PD Therapy in Mammalian Models

MJFF Rapid Response Innovation Award 2010, Standaert (Subaward PI), Gendelman (PI) 10/1/10 – 9/30/11
Michael J. Fox Foundation
Biomarkers and Immunotherapy for Parkinson's Disease
Role: Subaward PI

MJFF Target Validation 2009, Standaert (PI) 6/30/07 – 12/31/11
Michael J. Fox Foundation for Parkinson Research
Validation of VPS41, a Protein Involved in Lysosomal Trafficking, as a Target for Parkinson's Disease Therapy

RESEARCH & RELATED Other Project Information

OMB Number: 4040-0001
Expiration Date: 6/30/2016

1. Are Human Subjects Involved? ☐ Yes ☒ No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☐ No

If yes, check appropriate exemption number. ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

If no, is the IRB review Pending? ☐ Yes ☐ No

IRB Approval Date:

Human Subject Assurance Number:

2. Are Vertebrate Animals Used? ☒ Yes ☐ No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ☒ Yes ☐ No

IACUC Approval Date:

Animal Welfare Assurance Number: A3255-01

3. Is proprietary/privileged information included in the application? ☐ Yes ☒ No

4.a. Does this Project Have an Actual or Potential Impact - positive or negative - on the environment? ☐ Yes ☒ No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

5.a. If yes, please explain:

6. Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. Project Summary/Abstract Abstract.pdf Add Attachment | Delete Attachment | View Attachment

8. Project Narrative Project Narrative.pdf Add Attachment | Delete Attachment | View Attachment

9. Bibliography & References Cited References.pdf Add Attachment | Delete Attachment | View Attachment

10. Facilities & Other Resources Facilities.pdf Add Attachment | Delete Attachment | View Attachment

11. Equipment Equipment.pdf Add Attachment | Delete Attachment | View Attachment

12. Other Attachments Add Attachments | Delete Attachments | View Attachments ☒

Project Summary/Abstract

Frontotemporal dementia (FTD) is a progressive, fatal neurodegenerative disorder in which patients suffer personality changes, social withdrawal, and disinhibition. There is currently no treatment for this disease. Loss-of–function mutations in progranulin (*GRN*) that cause progranulin deficiency are a major genetic cause of FTD (5-10% of all cases). *Grn*$^{+/-}$ and *Grn*$^{-/-}$ mice are an animal model of progranulin deficiency, and may model some of the behavioral and neuronal dysfunction seen in FTD. Both *Grn*$^{+/-}$ and *Grn*$^{-/-}$ mice develop abnormal social behavior, conditioned fear deficits, and amygdala dysfunction around 6 months of age. *Grn*$^{-/-}$ mice also develop lipofuscinosis that may model neuronal ceroid lipofuscinosis, which occurs in patients homozygous for loss-of-function *GRN* mutations. The mechanism by which progranulin deficiency causes neuronal dysfunction is unknown, and is a key gap in our understanding of FTD. *Grn*$^{+/-}$ mice may be a useful model to address this question. In preliminary studies, we observed elevated phosphorylation of ribosomal protein S6 (Ser235/236) and Akt (Ser473) in the amygdala of *Grn*$^{+/-}$ mice. These data suggest increased signaling in the mTOR pathway, which causes abnormal social behavior in other mouse models. **The goal of this proposal is to investigate the hypothesis that progranulin deficiency causes abnormal social behavior, conditioned fear, and amygdala dysfunction through elevated mTOR signaling.** We will investigate this hypothesis using *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice. In **aim 1** we will determine if increased mTOR signaling causes abnormal behavior and amygdala dysfunction in progranulin-deficient mice. First, we will measure phosphorylated and total levels of mTOR pathway signaling molecules (p-Akt, p-mTOR, p-S6 kinase, and p-S6) in FTD-associated brain regions (amygdala and prefrontal cortex) and a region not expected to be affected (cerebellum) in *Grn*$^{+/+}$ and *Grn*$^{+/-}$ mice at ages before (3 months), during (5 and 7 months) and after (9 months) the transition to abnormal behavior. We will then determine if inhibiting mTOR signaling will prevent or reverse the phenotype of *Grn*$^{+/-}$ mice. Mice will be fed either a control or a rapamycin-supplemented diet for four weeks before (age 5-6 months) or after (age 9-12 months) the emergence of abnormal behavior. Immediately after this four week period, the mice will be tested for abnormal behavior and amygdala dysfunction. Amygdala function will be tested by measuring c-Fos expression after exposure to a novel, social environment. Inhibition of mTOR signaling will be confirmed by western blotting of cortex and amygdala samples. In **aim 2** we will investigate whether increasing progranulin levels with an AAV-*Grn* vector will normalize behavior, amygdala function, and mTOR signaling in *Grn*$^{+/-}$ mice. We will infuse AAV-*Grn* or AAV-*Gfp* into the prefrontal cortex and amygdala of *Grn*$^{+/+}$ and *Grn*$^{+/-}$ before (age 5-6 months) or after (age 9-12 months) the emergence of abnormal behavior. Behavior, amygdala function, and mTOR signaling will be tested four weeks after AAV injection, using the assays described in aim one.

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Project Narrative

Frontotemporal dementia (FTD) is a devastating neurodegenerative disease in which patients experience personality changes, social withdrawal, and early death. This project investigates the molecular mechanisms by which progranulin deficiency causes FTD. Successful completion of this project could facilitate development of new therapies for FTD, a disease for which there are currently no effective treatments.

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Biology. 2010;24(12):4639-47. doi: 10.1096/fj.10-161471. PubMed PMID: 20667979; PubMed Central PMCID: PMC2992364.
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Facilities and Resources

Laboratory: The Roberson laboratory occupies approximately 1550 square feet of recently constructed space on the 11th floor of the Shelby Interdisciplinary Biomedical Research building. The lab includes two bays of bench space, a suite for trainee desks, and five rooms (ranging from 100–185 square feet) designated for electrophysiology rigs, microscopy, and a BSL2-rated tissue culture facility. Additional shared spaces are nearby, including cold rooms, a dishwashing facility with two autoclaves, and conference and seminar rooms. The Shelby building is centrally located on the UAB School of Medicine campus and houses multidisciplinary programs in neuroscience, immunology, diabetes, and biomedical engineering. The 9th-11th floors comprise the Evelyn F. McKnight Brain Institute at UAB and are allocated to most of the primary faculty in the Department of Neurobiology, other labs in neuropharmacology and the Center for Neurodegeneration and Experimental Therapeutics (CNET), and several of the Neuroscience Blueprint Cores. The Cellular and Synaptic Physiology Core, containing 2 patch rigs and 7 field recording rigs, is immediately adjacent to the Roberson lab.

Animal: Experimental animals will be housed in the Research Support Building (RSB) attached to the Shelby building, in state-of-the-art space completed in 2008. The RSB facility is operated by the UAB Animal Resources Program and its full time veterinarians and veterinary technicians. Adjacent to the Roberson lab mouse housing is a 1200-sq-ft Behavior Core facility, with 11 separate testing rooms, fully equipped with behavior testing equipment. Also within the space are procedure rooms equipped for perfusion and necropsy. The Roberson lab also has its own dedicated surgery suite equipped for stereotaxic surgery with isoflurane anesthesia. All research involving animals at UAB is reviewed by the Institutional Animal Care and Use Committee to ensure compliance with federal, state and local government regulations and animal welfare organization guidelines. Animal research at the University of Alabama at Birmingham is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

Computer: Each of the 8 trainee desks is equipped with a Dell desktop running Microsoft Office suite, with four additional desktops in the lab supporting other equipment. The lab has licenses for Adobe Creative Suite, GraphPad Prism, and SPSS for data analysis. The lab maintains a color laser printer, Epson flatbed scanner with transillumination, and two Dell PowerEdge R410 servers with 2.5 TB of space for data storage. The Shelby building is fully equipped with both wired and WiFi networks.

Office: Dr. Roberson has two offices on the 11th floor of the Shelby building, including a 100-sq-ft space within his laboratory and a 145-sq-ft office a few steps down the hall, adjacent to those of other investigators on the floor. Each is equipped with a Windows desktop and printer and one contains a dedicated fax machine.

Institutional Support: The University provides a number of technical and career development resources that will be helpful in the current project. The University contains machine, electrical, and plumbing shops in addition to the department of biomedical engineering. Numerous core facilities in addition to those described here are provided by the Alabama Neuroscience Blueprint Core Center (http://www.alneurosciencecenter.uab.edu) and other core facilities at UAB (http://www.uab.edu/uasom/research/resources_corelist.htm). The University also provides career development opportunities to postdoctoral trainees through the Office of Postdoctoral Education (OPE). OPE provides classes and career development awards to trainees as described in the training plan.

Intellectual Rapport: The Roberson laboratory benefits from Dr. Roberson's dual appointments in the Dept. of Neurobiology and CNET in the Dept. of Neurology. As mentioned above, the laboratory is housed in the same building with labs from both the Dept. of Neurobiology and CNET. Members of the laboratory regularly attend seminars from both groups, and attend a monthly CNET lab meeting. This creates an intellectual environment rich with expertise in both basic science and clinical aspects of neuroscience. The Roberson lab regularly collaborates with investigators in both areas. An additional benefit of this environment is the broad range of technical expertise available to trainees.

Equipment

General Laboratory Equipment: The Roberson laboratory houses a 25-cu-ft –86°C freezer, 2 upright –20°C freezers, a 45-cu-ft 4°C chromatography refrigerator, 2 under-counter refrigerators, convection oven, Eppendorf 5424 and 5430 centrifuges, refrigerated thermomixer, 2 nutating rotators, orbital shaker, rotisserie mixer, 8 sets of LTS pipettes, 2 sets of multi-channel pipettes, 3 electronic pipettes (single and multi-channel), water bath, Milli-Q Gradient water purification system, basic and analytical balances, pH meter, and a fume hood. Each bench has a vortex, picofuge, Eppendorf Repeater Plus pipette, Pipet-Aid, heat/stir plate, and digital heat block. A 72-sq-ft shared cold room containing a sonicator is directly adjacent. Shared autoclaves and an ice maker are nearby on the same floor.

Molecular Biology and Biochemistry: The Roberson laboratory houses a Nanodrop 2000c spectrophotometer, Bio-Rad C1000 PCR machine, Thermo Precision incubator, 4 NuPAGE mini-gel systems, Bio-Rad Protean midi-gel system, 4 horizontal electrophoresis boxes (mini, midi, and maxi size), 3 electrophoresis power supplies, UV light source, microwave oven, and film cassettes. One bay in the lab contains a shared LI-COR Odyssey imaging system. Shared equipment in the McKnight Brain Institute on adjacent floors includes a Tecan Sunrise microplate reader, Avanti J25 centrifuge, Optima L100K ultracentrifuge, LS6500 scintillation counter, SpeedVac, BioRad gel imager, and film developer.

Histology: The Roberson laboratory houses a Leica SM2000R sliding microtome with Physitemp BFS-30MP freezing stage, Nikon Ni-E motorized imaging system with dual cameras (Clara E interline high-resolution CCD and Nikon DS-FI2 color camera), Zeiss Stemi 2000-C stereo zoom microscope, Nikon E200 upright microscope, McIlwain tissue chopper, and a peristaltic pump for perfusions. The High Resolution Imaging Facility downstairs has digital upright and inverted microscopes, 2 laser scanning confocal microscopes, and an FEI-Tecnai T12 Spirit TWIN electron microscope. Shared equipment in the Center for Neurodegeneration and Experimental therapeutics includes 2 Leica cryostats, 2 Microbrightfield StereoInvestigator systems for unbiased stereology and morphometric analysis, Arcturus Veritas laser capture microdissection system, and Alpha-Innotech FluorChem HD-2 imaging system.

Cell Culture: The Roberson laboratory houses a 185-sq-ft cell culture room with a laminar flow hood, 2 Thermo 3110 water-jacketed incubators, Nikon TE2000-S inverted fluorescent microscope with DS-QI1 cooled CCD camera, Eppendorf 5702 centrifuge, upright freezer/refrigerator, and water bath. Shared equipment in the Center for Neurodegeneration and Experimental therapeutics includes a Carl Zeiss Cell Observer high-speed live cell imaging system and liquid nitrogen tank.

Stereotaxic Surgery: The Roberson laboratory has its own dedicated surgery suite for performing stereotaxic surgeries. The suite contains a Kopf dual-arm digital stereotaxic frame, a Harvard Apparatus syringe pump, a Kopf stereotaxic drill, and a Parker Scientific isoflurane anesthesia device including a vaporizer and non-rebreathing circuit.

Electrophysiology: The Roberson laboratory houses 2 field electrophysiology rigs, each with dual stimulating and recording electrodes, enabling simultaneous recordings from four slices. Each rig consists of a Dell laptop running pCLAMP10, Digidata 1440 digitizer, A-M Systems model 1800 2-channel amplifier, ALA Scientific stimulus isolator, interface slice chamber, Leica S6E stereozoom microcope, and four micromanipulators on a vibration isolation table with Faraday cage, Warner temperature control unit and Rainin peristaltic pump. Next door is a shared Vibratome and electrode puller. The Neuroscience Blueprint core has a Data Sciences International telemetric EEG system.

Behavior: In the Behavior Core facility directly adjacent to the Roberson lab mouse housing room are an elevated plus maze, 2 open fields, Gemini system for automated trials of active/passive avoidance learning, conditioned place preference system, startle and prepulse inhibition apparatus, automated rotorod, radial arm maze, Morris water maze, 4 fear conditioning boxes, CleverSys SocialScan system with capacity for 4 arenas, and 2 CleverSys GroupHousedScan stereo-view home-cage behavior monitoring systems. A second behavior core at UAB contains a Laboras automated behavior recognition system.

Additional Educational Information

UAB has a postdoctoral association and an office of postdoctoral education (OPE) to enhance the training and career development of its postdoctoral fellows. The OPE offers four courses that are each taught once per year. The courses are team taught by UAB faculty and staff, and cover grant writing, job skills, lab management, and clinical and translational research. Each course lasts around 10 weeks and meets for 3 hours once per week for a total of approximately 30 hours of training. In addition to these courses, OPE offers several career enhancement awards. UAB postdocs can apply for travel awards to conferences, as well as career enhancement awards of up to $1500 to fund attendance in external courses such as those offered at Wood's Hole or Cold Spring Harbor Laboratory. OPE also offers $5000 internship awards to fund internal or external internships for postdocs. The OPE hosts an annual postdoc research day to provide a forum for UAB postdocs to present oral presentations of their research, with cash prizes for the best presentations. This commitment to postdoctoral training has led to UAB being ranked 8th overall and first among public universities in The Scientist magazine's 2013 survey of best places to work for postdocs.

Statement provided by Erik Roberson

OMB Number: 4040-0010
Expiration Date: 9/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Alabama at Birmingham

DUNS Number: 0636907050000

* Street1: 1825 University Blvd, SHEL 1171

Street2:

* City: Birmingham

County: Jefferson

* State: AL: Alabama

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: 352942182

* Project/ Performance Site Congressional District: AL-007

Project/Performance Site Location 1

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:

DUNS Number:

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