



## **Alzheimer's Disease Research Grant Advisory Board**

Ed and Ethel Moore Alzheimer's Disease Research Program

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### **2018-2019 Report**

Ron DeSantis  
Governor

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## **ED AND ETHEL MOORE ALZHEIMER'S DISEASE RESEARCH PROGRAM INTRODUCTION AND OVERVIEW**

Alzheimer's disease is a debilitating brain disease that affects approximately 5.7 million Americans, including 540,000 Floridians, over the age of 65.<sup>4</sup> It is estimated that by 2025, over 720,000 seniors will be living with this disabling disease in the state of Florida.<sup>1</sup> Alzheimer's disease is the sixth leading cause of death in Florida. Additionally, in 2017 it is estimated that 13.5% of Floridians over the age of 65 are likely to have Alzheimer's disease.

According to the National Institute on Aging, a subdivision of the National Institutes of Health, Alzheimer's disease is characterized as an "irreversible, progressive brain disorder that slowly destroys memory and thinking skills, and, eventually, the ability to carry out the simplest tasks."<sup>1</sup> It is the most common cause of dementia among the senior population, with symptoms interfering with normal daily life activities, including loss of thinking, memory, and reasoning abilities. African Americans are twice as likely and Hispanics are one and a half times as likely as older whites to have Alzheimer's disease and other dementias.<sup>2,3,7,8</sup> The prevalence is also higher among women compared to men; two-thirds of Americans with Alzheimer's disease are women.<sup>1</sup> Although there is no known cure, innovative research may provide hope for effective and novel treatment for this incapacitating disease.

To combat these startling statistics, the 2014 Florida Legislature created the Ed and Ethel Moore Alzheimer's Disease Research Program (Program) that was signed and enacted by Governor Rick Scott. This Program is managed by the Florida Department of Health. The long-term goals of this Program are to:

- a) Improve the health of Floridians by researching improved prevention measures, diagnosis methods, treatments, and cures for Alzheimer's disease.
- b) Expand the foundation of knowledge relating to the prevention, diagnosis, treatment, and cure for Alzheimer's disease.
- c) Stimulate economic activity in the state in areas related to Alzheimer's disease research.

Annually, the Alzheimer's Disease Research Grant Advisory Board submits a fiscal year progress report by February 15<sup>th</sup>, as required by section 381.82, Florida Statutes. With the additional reporting requirements resulting from legislative change effective July 1, 2016, this report provides current findings on the return on investment resulting from the state supported research grant funding.

## **ALZHEIMER'S DISEASE RESEARCH GRANT ADVISORY BOARD**

### **Ed and Ethel Moore Alzheimer's Disease Research Program Overview**

The Ed and Ethel Moore Alzheimer's Disease Research Program was created by the 2014 Florida Legislature and signed by Governor Rick Scott. The purpose of this program in the Florida Department of Health (Department) is to fund research leading to the prevention of, or cure for, Alzheimer's disease. The long-term goals of the program are to:

- a) Improve the health of Floridians by researching better prevention, treatments, diagnosis tools, and cures for Alzheimer's disease.
- b) Expand the foundation of knowledge relating to the prevention, diagnosis, treatment, and cure of Alzheimer's disease.
- c) Stimulate economic activity in the state in areas related to Alzheimer's disease research.

### **Alzheimer's Disease Research Grant Advisory Board**

On October 1, 2014, the State Surgeon General and Secretary of Health, appointed 11 members to the Alzheimer's Disease Research Grant Advisory Board (Advisory Board). The Advisory Board authorized in Section 381.82, Florida Statutes, consists of: two gerontologists, two geriatric psychiatrists, two geriatricians, two neuroscientists, and three neurologists.

The Advisory Board advises the State Surgeon General as to the scope of the research program and shall submit its recommendations for proposals to be funded to the State Surgeon General by December 15 of each year. Grants and fellowships shall be awarded by the State Surgeon General, after consultation with the Advisory Board, on the basis of scientific merit. Other responsibilities of the Advisory Board may include, but are not limited to, providing advice on program priorities and emphases; assisting in the development of appropriate linkages to nonacademic entities, such as voluntary organizations, health care delivery institutions, industry, government agencies, and public officials; and developing and providing oversight regarding mechanisms for the dissemination of research results.

### **Alzheimer's Disease Research Grant Advisory Board Membership**

The names and positions of each Alzheimer's Disease Research Grant Advisory Board Member, as of December 12, 2018, are listed below (Biographical Statements or Curriculum Vitae are available upon request):

#### **Gerontologists:**

Leilani Doty, PhD, Chair

Associate Director of Programs, Central and North Florida Chapter of Alzheimer's Association

Jacqueline C. Wiltshire, PhD,

Assistant Professor, Health Policy and Management, College of Public Health, University of South Florida

#### **Geriatric Psychiatrists:**

Josepha A. Cheong, MD

Professor of Psychiatry and Neurology, University of Florida and Chief, Consult-Liaison Psychiatry, Malcom Randall Veterans Affairs Medical Center

Uma Suryadevara, MD, FAPA

Assistant Professor of Psychiatry and Program Director, Geriatric Psychiatry Fellowship Program, College of Medicine, University of Florida

**Geriatricians:**

Mariana B. Dangiolo, MD

Assistant Professor of Family Medicine and Geriatrics, College of Medicine, University of Central Florida

Niharika Suchak, MBBS, MHS, FACP

Associate Professor, Department of Geriatrics, College of Medicine, Florida State University

**Neuroscientists:**

Eunsook Yu Lee, PhD

Professor, College of Pharmacy, Florida Agricultural and Mechanical University

Leonard Petrucelli, PhD, Assistant Chair

Chair, Department of Neuroscience and Professor of Neuroscience, Mayo Clinic Jacksonville

**Neurologists:**

Mark Brody, MD, CPI

President and Founder, Brain Matters Research

Neill Graff-Radford, MD

Professor of Neurology, Department of Neurology, Mayo Clinic Jacksonville

Hal S. Pineless, DO, FACN

President and Owner, NeuroCare Institute of Central Florida, PA

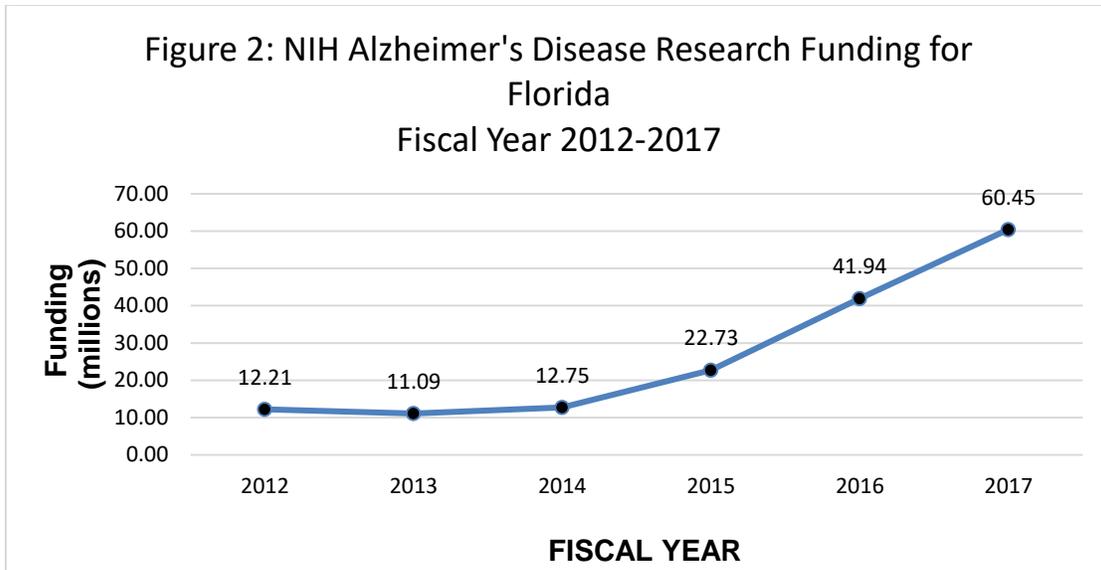
## NATIONAL INSTITUTES OF HEALTH STATE RANKING IN TOTAL AMOUNT OF ALZHEIMER'S DISEASE RESEARCH FUNDING

Between fiscal years 2012-2014, Florida researchers were awarded \$12,017,087 from the National Institutes of Health (NIH) to perform Alzheimer's disease research, ranking 12<sup>th</sup>, 13<sup>th</sup> and 11<sup>th</sup> in national federal funding, respectively, per the NIH's National Center for Health Statistics. By fiscal year 2015, NIH funding in the state of Florida nearly doubled to \$22,729,691 and nearly tripled in fiscal year 2017, to \$60,454,514 (Figure 2). **Since the inception of the Ed and Ethel Moore Alzheimer's Disease Research Program in 2014, Florida has increased its national ranking to fifth place and its total federal funding for Alzheimer's disease research increased by \$18,512,085 in the 2017 fiscal year** (Figure 1). Florida is the only state in the southeastern United States to be ranked in the Top 10. This significant increase in federal research dollars can be attributed to the foundational support provided by the Ed and Ethel Moore Alzheimer's Disease Research Program for groundbreaking research and training. **Florida saw the 4<sup>th</sup> highest growth in new research funding, behind the states of Ohio, Michigan, and Georgia, and saw the highest funding gains of the Top 10 ranked states in 2017, more than doubled the rate of the 2<sup>nd</sup> ranked state, New York** (Figure 2 and 3).<sup>10</sup>

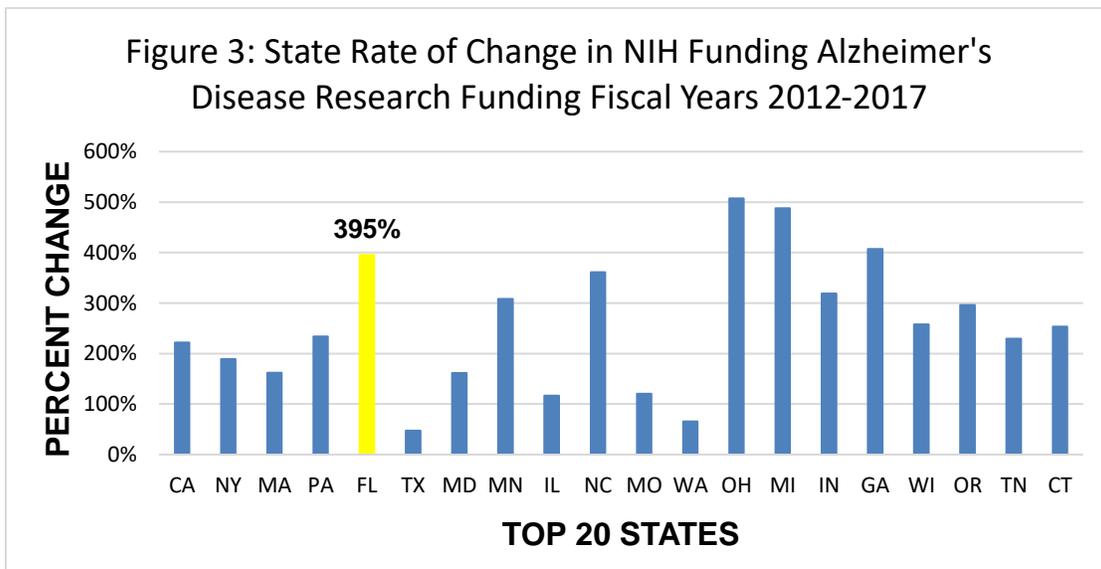
**Figure 1: National Institutes of Health Alzheimer's Disease Research State Funding and Rankings Fiscal Year 2017**

State	Total Funding	Rank
CA	\$303,940,202.00	1
NY	\$146,089,058.00	2
MA	\$119,691,161.00	3
PA	\$87,872,629.00	4
<b>FL</b>	<b>\$60,454,514.00</b>	<b>5</b>
TX	\$58,268,711.00	6
MD	\$58,197,381.00	7
MN	\$52,385,146.00	8
IL	\$48,255,860.00	9
NC	\$46,909,031.00	10
MO	\$43,651,001.00	11
WA	\$37,029,473.00	12
OH	\$30,435,899.00	13
MI	\$25,353,967.00	14
IN	\$24,332,385.00	15
GA	\$24,077,895.00	16
WI	\$17,716,803.00	17
OR	\$15,004,455.00	18
TN	\$14,030,929.00	19
CT	\$13,720,851.00	20

**Fig.1 NIH Research Funding from the 2018 Fiscal Year Reporting Period:** The top twenty ranked states in NIH funding for Alzheimer's disease is displayed. With over \$60.4 million in NIH funding, Florida is ranked 5<sup>th</sup> in the nation. *Source: National Center for Health Statistics, National Institutes of Health 2018*



**Fig. 2 NIH Research Funding Trends in Florida Fiscal Year 2012-2017:** This chart illustrates the recent trends in federal funding for Alzheimer’s disease research in the state of Florida. Following three years of relative stability in funding levels, fiscal years 2015-2017 saw a vast increase of funding leading to a 474% increase of funding since 2014. In fiscal year 2017, Florida’s total federal funding increased by \$18.5 million. *Source: National Center for Health Statistics, National Institutes of Health 2018*



**Fig. 3 Change in NIH Research Funding in the Top 20 States Fiscal Years 2012-2017:** This graph displays the rate of change in federal Alzheimer’s disease research funding for the Top 20 states for fiscal years 2012-2017. Among the Top 10 ranked states in NIH funding for Alzheimer’s disease, Florida saw the fourth highest funding gains since 2012 (395%). Between 2016 and 2017, Florida’s NIH funding for Alzheimer’s disease grew by 44.1% and was ranked fifth for total funding. *Source: National Center for Health Statistics, National Institutes of Health 2018*

## **PROGRESS TOWARD PROGRAMMATIC GOALS**

The Ed and Ethel Moore Alzheimer's Disease Research Grant Advisory Board's research agenda emphasizes the creation of intra-state research collaborations to make progress toward Florida becoming the premier state for Alzheimer's disease prevention, diagnosis, treatment, and ultimately, cure for this disease. The research agenda has five research priority areas that are outlined in the Funding Opportunity Announcement (FOA) and are listed below:

- The social/behavioral aspects of care, as well as, palliative and end of life care for people with Alzheimer's disease
- Elucidation of the basic science relating to the disease
- Consortium grants between Florida-based institutions to augment established research networks and promote novel networks
- Epidemiological studies examining the prevalence, incidence, and risk factors of the disease with priority given to studies examining health disparities
- Fellowships aimed at enhancing the workforce of Florida's researchers working on Alzheimer's disease

This fiscal year, the legislature provided \$5 million for research grants. Appendix A details all newly awarded grants and Appendix B details all active grants in 2018-2019. Information regarding progress reports, follow on funding, publications and patents of each active grant is found in Appendix B.

### **THE HEALTHY BRAIN INITIATIVE: THE PUBLIC HEALTH ROAD MAP FOR STATE AND NATIONAL PARTNERSHIPS**

In 2017, the Florida Department of Health was one of five states to receive a grant from the Alzheimer's Association, in collaboration with the Association of State and Territorial Health Officials (ASTHO), and in partnership with the Centers for Disease Control and Prevention's (CDC) Alzheimer's Disease and Healthy Aging Program, to fund and support state public health agencies to address Alzheimer's disease, dementia, and cognitive health. The grant funds implementation of the Road Map and emphasizes the role of state and local public health agencies and partners in promoting cognitive functioning, addressing cognitive impairment and Alzheimer's disease, in addition to, helping meet the needs of caregivers. The Road Map supports 35 action items in the four domains of the CDC's Essential Public Health Services: assure a competent workforce, educate and empower the nation, monitor and evaluate, and develop policy and mobilize partnerships.

The first-ever Florida Health Alzheimer's Disease Awareness and Research Symposium was held June 7 – 8, 2018 and was made possible through this grant. Over 250 researchers, caregivers, and health professionals, working in the field, attended the event. It was an opportunity to share research findings, increase research collaboration, and provide education for the community. The Florida Health Alzheimer's Disease Awareness and Research Symposium aligns with the Department's strategic objectives and will assist in implementing

applied solutions to address Alzheimer's disease, dementia, and cognitive health in Florida. The Florida Chapters of the Alzheimer's Association, Florida Department of Elder Affairs, and the Florida Hospital Neuroscience Institute are diligent partners in the implementation of this initiative. The Florida Department of Health will continue to develop effective partnerships with local and state organizations to enhance the resources and information vital for diminishing this disabling disease.

## **RECOMMENDATIONS FROM THE ALZHEIMER'S DISEASE RESEARCH GRANT ADVISORY BOARD TO FURTHER THE MISSION OF THE PROGRAM**

This has been a successful year for the Ed and Ethel Moore Alzheimer's Disease Research Grant Program with funding to award \$5,000,000 to 30 outstanding research projects this fiscal year. Without this support, the eminent scientific advancements and discoveries in Alzheimer's disease would not be possible.

Statutory change is needed to allow for reimbursement of travel expenses resulting from Advisory Board in-person meetings. Face-to-face communication intensifies the exchange of information to allow for effective strategic planning and in-depth communication about critical research issues. In-person meetings engage full attention, build trust and credibility of the Advisory Board and strengthen collaboration on ideas from their expertise that may be translated into research priorities for grant applications. These meetings can fuel more and varied planning to hone the Research Agenda and the Funding Opportunity Announcement documents to identify unaddressed needs and challenges of researchers as they work to discover or enhance preventions, care, cures, and treatments of Alzheimer's disease.

The Alzheimer's Disease Research Grant Advisory Board thanks the Governor and the Florida Legislature for their continuous support as we work together to eradicate Alzheimer's disease.

**APPENDIX A**  
**FISCAL YEAR 2018-2019 NEWLY AWARDED GRANTS (effective December 15, 2018)**

Grant #	Organization	PI Name	Project Title	Award Amount
9AZ01	Florida Atlantic University	Rosselli, Monica	Neuroimaging and Sensitive Novel Cognitive Measures in Detection of Early Alzheimer's Disease in Bilingual and Monolingual Hispanic Americans	\$ 235,018.60
9AZ02	Florida Atlantic University	Van Praag, Henriette	The Role of Exercise-Induced Systemic Factors in Alzheimer's Disease.	\$ 237,500.00
9AZ03	Florida Atlantic University	Tappen, Ruth	Fit2Drive: Development and Testing of a Driver Risk Predictor for Individuals with AD	\$ 237,500.00
9AZ04	Florida Atlantic University	Galvin, James	Peripheral Biomarkers to Define the Amyloid, Tau, Neurodegeneration (ATN) Research Framework	\$ 94,709.30
9AZ05	Florida Atlantic University	Ghoraani, Behnaz	Technology-based Systems to Measure Dual-task (motor-cognitive) Performance as a Biomarker for Early Detection of Alzheimer's Disease	\$ 95,000.00
9AZ06	Florida Atlantic University	Wei, Jianning	Effect of Neuronal Activity on Synaptopathy in Alzheimer's Disease using a Novel Multi-electrode Microfluidic Platform	\$ 94,998.82
9AZ07	Florida International University	Burke, Shanna	Shared Neuroanatomical Models of Psychiatric Conditions and Alzheimer's Disease Spectrum Disorders: The Effects of Depression, Anxiety, and Sleep Disturbance and Associated Changes in Brain Morphology Leading to Alzheimer's Disease.	\$ 237,500.00
9AZ08	Mayo Clinic Jacksonville	Ebbert, Mark	Identifying Functional Mutations in Top Alzheimer's Disease GWAS Genes using Long-read Sequencing in Brain Tissue	\$ 237,500.00
9AZ09	Mayo Clinic Jacksonville	Li, Yonghe	Therapeutic Roles of Surrogate Wnt Agonist in Alzheimer Disease	\$ 95,000.00
9AZ10	Mayo Clinic Jacksonville	Springer, Wolfdieter	Validation of Novel, Selective Autophagy Biomarkers in Alzheimer Disease	\$ 87,181.82
9AZ11	Mount Sinai Medical Center	Greig-Custo, Maria	Impact of the MindSight Training Program on Patients with MCI and Early Stage Dementia	\$ 237,500.00
9AZ12	University of Central Florida	Wharton, Tracy	The Florida REACH Translation Project: Translating an EBP for an Outpatient Clinical Setting to Reach Diverse Community Members	\$ 94,998.91
9AZ13	University of Florida	Garvan, Cynthia	Is Cortisol Really a Factor in Cognitive Decline?	\$ 95,000.00
9AZ14	University of Florida	Maraganore, Demetrius	Utilizing Data from the Electronic Medical Record to Predict Alzheimer's and Dementia Risk	\$ 237,500.00

9AZ15	University of Florida	Smith, Glenn	Association of PET Amyloid Status with Cognitive and Functional Outcomes of Behavioral Interventions in Mild Cognitive Impairment	\$ 237,500.00
9AZ16	University of Florida	Mitchell, Gordon	The Two Faces of Hypoxia in Alzheimer's Disease	\$ 237,497.89
9AZ17	University of Florida	Giasson, Benoit	Mechanisms of Abnormal Neuronal Tau Accumulation, Interactions with Amyloid-beta and Pathological Sequelae.	\$ 237,500.00
9AZ18	University of Florida	Weisbrod, Neal	Responses to a Standardized Approach to Advance Care Planning in Cognitive Disorders Clinic	\$ 87,181.82
9AZ19	University of Florida	Price, Catherine	Impact of Total Knee Replacement Surgery on Trajectory of Cognitive Decline in Individuals with Mild Cognitive Impairment (MCI)	\$ 237,080.10
9AZ20	University of Miami	Govind, Varan	Role of Gut Microbiota on the Brain Metabolism, Cognition, Immune Function and Inflammation in Alzheimer's Disease: Novel Biomarkers and Understanding Mechanisms	\$ 87,181.82
9AZ21	University of Miami	Curiel, Rosie	Postdoctoral Research Fellowship In Neuropsychology	\$ 84,301.00
9AZ22	University of Miami	Harvey, Philip	Postdoctoral Fellowship in Cognitive Neuroscience and Neuropsychology	\$ 87,830.00
9AZ23	University of Miami	Brown, Scott	Impacts of Neighborhood Greenness & Greening Initiatives on Alzheimer's Disease in Medicare Beneficiaries	\$ 95,000.00
9AZ24	University of Miami	Loewenstein, David	Middle-aged Offspring of Late Alzheimer's Probands: Novel Cognitive and Biomarker Assessment	\$ 237,171.38
9AZ25	University of Miami	Rundek, Tatjana	Brain Vascular Imaging Phenotypes, Vascular Comorbidities and the Risk for Alzheimer Disease: The Florida VIP Study of AD Risk	\$ 237,500.00
9AZ26	University of South Florida	Dobbs, Debra	Palliative Care Education in Assisted Living for Care Providers of Residents with Dementia	\$ 237,496.20
9AZ27	University of South Florida	Conner, Kyaien	A Pilot Study to Examine the Impact of an African Drumming for Dementia Program on African Americans with Mild Cognitive Impairment and Early Alzheimer's Disease and their Caregivers	\$ 95,000.00
9AZ28	University of South Florida	Meng, Hongdao	Visually-Assisted Mindful Music Listening Intervention for Persons Living with Dementia and their Caregivers: A Pilot Study	\$ 94,860.35
9AZ29	University of South Florida	Webster, Jack	Intracellular anti-Tau Proteins Engineered on a Hyperthermophilic Scaffold	\$ 95,000.00
9AZ30	University of South Florida	Bennett, Crystal	Impact of Adapted Dance on Mood and Physical Function among Alzheimer's Disease Assisted Living Residents	\$ 94,991.99

**NEW GRANTS FISCAL YEAR 2018-2019 (Effective December 15, 2018)**  
(Funding Year 2018-2019)

1. **Grant #9AZ01:** Neuroimaging and Sensitive Novel Cognitive Measures in Detection of Early Alzheimer's Disease in Bilingual and Monolingual Hispanic Americans

**Principal Investigator:** Monica Rosselli, PhD

**Organization:** Florida Atlantic University

**Abstract of Proposed Research:** The prevalence of dementia in Hispanics/Latinos is greater than in European Americans (EAs). Alzheimer's disease (AD) results from genetic and environmental factors which are more complex in the Hispanic group due to the influence of lower levels of education, economic/immigration factors, language proficiency, and culture, in the development and progression of the disease. Low levels of education, low socioeconomics, and immigration status are risk factors for enhancing AD, whereas others, such as bilingualism, seem to offer a protective factor against dementia. The interaction between these factors with biomarkers in the progression of AD is not understood. Furthermore, Hispanic populations have been greatly understudied regarding early detection of memory loss using novel cognitive measures related to volume reduction in brain areas for late onset AD. This study will overcome this gap by evaluating the relationships between brain imaging (structural volumes and brain connectivity) and cognitive tests that are sensitive to early AD among monolingual and bilingual Hispanics with amnesic mild cognitive impairment (aMCI) and normal controls (NC). Results will be compared to performance in equivalent groups of EAs; Dr. Rosselli and associates will measure proactive semantic interference (PSI), recovery from proactive interference, and correlate cognitive scores with cortical thickness of brain areas susceptible to AD and with the integrity of brain tracks. The influence of other environmental factors, such as socioeconomics, immigration, and level/quality of education will be included as predictors of cortical thickness in association to cognitive test performance using regression models. This proposal will use the existing infrastructure and collaborations between five Florida institutions, Florida Atlantic University (FAU), University of Miami (UM), University of Florida (UF), Albizu University and Mount Sinai Medical Center (MSMC), established during the current NIH grant to the Florida Alzheimer's Disease Research Center (ADRC) and will create a bridge with another NIH grant awarded to researchers at UM. This proposed work will complement an ongoing NIH longitudinal study at the ADRC that does not include the MRI technique analysis of Diffusion Tensor Imaging (DTI) to establish structural patterns of brain connectivity. Recent papers by their group demonstrated that failure to recover from PSI, based on a novel cognitive test, could distinguish between individuals with MCI and cognitively normal elders. A critical finding was that failure to recover from PSI was highly associated with decreased volumes in the brain areas affected by AD. These findings were mainly obtained in samples of individuals with European American ethnic backgrounds. Also, recent analyses of their data showed that Hispanic bilinguals significantly outperformed monolinguals on two recall measures, suggesting that bilinguals, by using two languages regularly, develop a different and perhaps more efficient semantic association system that influences verbal recall. However, they did not have monolingual Hispanics (Spanish speakers) in the published study. In the current investigation, they propose to study the interaction of language, culture, and cognitive factors with brain biomarkers in an additional 40

Hispanic monolingual Spanish speakers, 40 Hispanic Spanish/English bilinguals, and 40 EA English monolinguals older adults.

2. **Grant #9AZ02:** The Role of Exercise-Induced Systemic Factors in Alzheimer's Disease.

**Principal Investigator:** Henriette van Praag, PhD

**Organization:** Florida Atlantic University

**Abstract of Proposed Research:** With the increase in human lifespan, more aging-related cognitive disorders, including Alzheimer's disease (AD) are being diagnosed. In the absence of effective medications, physical activity is a simple, low-cost intervention that may prevent or delay the onset of memory loss. It used to be thought that neurons could not be added or replaced in the adult brain. It is now known that populations of residual central nervous system (CNS) stem cells give rise to new neurons. Dr. Van Praag and associates were the first to show that running increases the production of new neurons in the hippocampus, a region important for learning and memory. Since this discovery, they and others have shown that running enhances synaptic plasticity, performance on learning tasks, growth factor levels and vasculature in the rodent brain. Moreover, in mouse models of AD there is accumulating evidence that running counteracts amyloid-beta ( $A\beta$ ) production, reduces neuroinflammation, benefits learning and increases adult neurogenesis. In humans, there is complementary evidence that exercise improves cognitive function, hippocampal volume and cerebral blood flow and may slow the progression of memory loss in patients with minimal cognitive impairment and AD. The underlying mechanisms for these effects remain unclear. In particular, the systemic, metabolic and peripheral triggers that elicit these processes have only been recently begun to be explored. Such research suggests that blood-borne systemic factors can counteract age-related decline of adult neurogenesis and brain function. Upon activation by exercise, skeletal muscle releases factors that circulate and communicate with the brain. Their studies indicate that among the key signals that arise from muscle, a class of molecules called myokines, can increase CNS stem cell differentiation, and may be important for improvements in memory function in mice and humans. It is proposed to determine whether myokines support the effects of exercise and exercise-mimetics on brain function and behavior using a mouse model of Alzheimer's Disease. Specifically, they will (Aim 1) compare the effects of voluntary wheel running, a compound that activates muscle energy metabolism, the AMP-kinase agonist AICAR, and the novel myokine Cathepsin B, on memory function in an AD mouse model (APP<sup>swe</sup>/PS1 transgenic mice). They will evaluate (Aim 2) adult hippocampal neurogenesis, brain-derived neurotrophic factor (BDNF) levels and synaptic plasticity after these manipulations. In addition, they will assay  $A\beta$  and tau levels in the hippocampi and cortices of the subjects. Moreover, they propose (Aim 3) to discover novel myokines that may aid brain function. The researchers will compare the effects of conditioned media secreted by wildtype and AD skeletal muscle cells derived from rodent and human subjects on neural stem cell differentiation in vitro. Proteomic analysis of the conditioned media will be performed, and potential candidate proteins will be studied in detail for their effects on neurogenesis. Together, these studies will add significantly to the understanding of the identity and role of molecules secreted by skeletal muscle cells that translate aerobic exercise to improved brain function and how they are modified by AD, providing important preclinical evidence as to whether novel therapeutic strategies based on myokines could be useful for AD patients.

3. **Grant #9AZ03:** Fit2Drive: Development and Testing of a Driver Risk Predictor for Individuals with AD

**Principal Investigator:** Ruth M. Tappen, EdD, RN, FAAN

**Organization:** Florida Atlantic University

**Abstract of Proposed Research:** It is well known that Alzheimer's disease (AD) and related chronic progressive dementias not only place individuals at risk for unsafe driving but eventually leave the impaired individual unable to drive. While individuals with AD certainly do evidence greater decline in driving performance than do unimpaired older adults, there is also substantial evidence that those in the earliest stages may be able to continue driving safely for some time. This is important for the large proportion of older adults who depend upon their personal automobile for transportation. Driving cessation has a profound effect on functional independence, self-esteem, mood, social life, ability to participate in community activities and ability to obtain everyday necessities and needed services. Family caregivers report that driving cessation is one of the most difficult decisions they encounter. When individuals with AD and their families first realize that the progressive cognitive impairment will eventually render driving unsafe for themselves and for others, they often find it difficult to weigh personal safety and the safety of others against the significant losses that come with driving cessation. Many begin to search for answers, often consulting their providers for guidance. Their Fit2Drive Calculator is designed to provide evidence-based support for providers' discussions with impaired individuals and their families on the decision to stop driving. To create Fit2Drive, Dr. Tappen and associates analyzed results of 290 driver evaluations conducted at FAU's Memory and Wellness Center finding that two brief tests, the Mini-Mental State Examination (MMSE) and Trail Making Test Part B (Trails B), provided an efficient and relatively strong prediction of ability to pass an on-road driving test which is considered the gold standard in testing driver ability. Limits of the current data and resulting Calculator include a very small number of unimpaired individuals in the database, thereby limiting predictive ability for those with little or no impairment, a small number of minority individuals tested and the need to further validate the Calculator before general use in clinical practice. This proposed study addresses these limitations. The proposed study will allow them to recalibrate the Fit2Drive calculator and obtain estimates of its diagnostic accuracy on a larger, more diverse sample as well as to test additional cognitive tests that may generate a more accurate prediction for individuals at every stage of Alzheimer's disease. Diagnostic accuracy refers to the quality of the information provided by the Calculator, that is, the test's ability to discriminate those with and without the ability to pass an on-road driving test. Both sensitivity and specificity will be tested. They will also explore if the addition of demographic variables such as age, gender and education improve the accuracy of this Fit2Drive model and which cognitive tests provide the most accurate prediction in the shortest amount of testing time. They will do this by recruiting an ethnically and racially diverse sample of 400 participants with varying levels of AD and non-AD testing. Once the Calculator's accuracy has been improved and rigorously tested, they will apply for NIH funds to support a translational study to test its application into clinical practice.

4. **Grant #9AZ04:** Peripheral Biomarkers to Define the Amyloid, Tau, Neurodegeneration (ATN) Research Framework

**Principal Investigator:** James E. Galvin MD, MPH

**Organization:** Florida Atlantic University

**Abstract of Proposed Research:** Alzheimer's disease (AD) affects millions of Americans presenting a significant public health challenge that will only increase as the US population ages. Inclusion criteria for AD clinical trials often require expensive and invasive biomarker confirmation to establish eligibility. A new "ATN" research framework characterizes individuals along the Alzheimer pathology continuum including biomarkers that capture amyloid (A), tau (T), and neurodegeneration (N). A major obstacle in early detection, treatment, and risk reduction is the absence of robust surrogate markers of amyloid, tau, and neurodegeneration pathology identifying at-risk individuals, prompting early intervention and trial eligibility, compounded by the availability, cost, acceptability, and invasiveness of current biomarker approaches. One strategy to overcome these challenges is to capitalize on two sources of peripherally available biomarkers to stage individuals. Plasma biomarkers (collaborating with MagQu Co Ltd) of amyloid and tau can provide the A and T of the framework, while biometric identification through the powerful technique of optical coherence tomography (OCT) may detect the N component of the framework. OCT is a medical imaging technique using near-infrared light to capture 3-D micrometer-resolution, three-dimensional imaging of cornea, lens, anterior chamber, retinal tissue, and retinal vasculature. Combined with plasma amyloid and tau measurements, ocular markers may provide early evidence of AD pathology. Embryologically, the eye is derived from the neuroepithelium (retina, ciliary body, iris, optic nerve), surface ectoderm (lens, corneal epithelium, eyelid), and the extracellular mesenchyme (sclera, cornea, blood vessels, muscles, and vitreous). While magnetic resonance imaging (MRI) techniques exist to explore neurodegeneration, and positron emission tomography (PET) and cerebrospinal fluid (CSF) analyses are available to study amyloid and tau, these procedures are expensive, invasive, and time-consuming. Dr. Galvin and associates propose an innovative study combining plasma measurements of amyloid (Ab40, Ab42) and tau (total tau, phosphotau) and OCT to model the ATN Framework and AD risk. They propose three Specific Aims: (1) Determine the baseline association between plasma and CSF biomarkers of amyloid and tau protein in a well characterized sample of older adults ranging from no cognitive impairment, subjective cognitive impairment, mild cognitive impairment, and very mild AD; (2) Characterize the baseline association between OCT and MRI markers of neurodegeneration; and (3) Evaluate the longitudinal change between baseline and 12-month plasma-OCT findings as a robust surrogate marker for risk of AD pathology. The Comprehensive Center for Brain Health has evaluated over 250 individuals in the past 18 months (5-year target = 500 active participants). The in-person comprehensive clinical, cognitive, behavioral, and functional assessments are modelled on the Uniform Data Set (UDS) 3.0 and includes OCT, videonystagmography, plasma biomarkers, Apolipoprotein E (ApoE) genotyping, and 3T MRI with FreeSurfer volumes. Their short-term goal is to investigate relationships between plasma-OCT markers of ATN compared with Gold Standard measurements. Their long-term goal is to validate combined plasma-OCT markers as robust biometric signatures to identify at-risk individuals, improve inclusion criteria and enrollment into AD clinical trials.

5. **Grant #9AZ05:** Technology-based Systems to Measure Dual-task (motor-cognitive) Performance as a Biomarker for Early Detection of Alzheimer's Disease

**Principal Investigator:** Behnaz Ghoraani, PhD

**Organization:** Florida Atlantic University

**Abstract of Proposed Research:** Alzheimer's disease (AD), affects over 5 million Americans, of which 10% are Florida residents with an annual cost of over \$2.5 billion. The prevalence of mild cognitive impairment (MCI), the prodromal phase of AD, is an estimated 21% for those over age 65, of which 75% will progress to AD. The sooner physicians/researchers are able to detect MCI, the sooner they are to intervene and slow, or perhaps even halt, the progression to AD. Patients with MCI are typically evaluated by cognitive testing and neurological examination to estimate risk and rate of decline. However, cognitive tests may not accurately predict progression and outside of academic settings, may have limitations when applied to general populations. There are also limits due to intra-individual variability compared with inter-individual normative values. Additionally, these extensive cognitive testing is generally not provided as part of routine care in the primary care setting or general neurologists offices. This could explain in part, why there is often a delay in diagnosis of cognitive impairment until the moderate stage. What is desperately needed are objective methods for in-home use that can detect individuals who are most at-risk for MCI and AD so that early intervention or prevention strategies can be initiated. One such method is to look at simultaneous assessment of motor and cognitive performance (known as dual-task performance) to detect at-risk individuals. Gait tests have been commonly used as the motor task component in dual-task assessments. Poor dual-task gait performance has been significantly associated with decreased executive and neuropsychological function and demonstrated to be predictive of AD and MCI. However, many clinics lack adequate space to safely perform gait measures. The goal of this study is to enable early detection of AD and its prodrome, MCI, by developing a dual-task monitoring system that can be employed outside of clinical settings and objectively track cognitive decline. The present objective towards their goal is to collect and analyze speech and ambulatory data from subjects over routine clinical visits so that they can measure declines in their motor-cognitive response. The research team will use healthy subjects as their control group and show that their algorithms can detect the diminishing motor-cognitive response with the greatest effect seen in those individuals with underlying neurodegenerative disease (Healthy Controls > MCI > AD). Their rationale is that their algorithms can integrate the speech and ambulatory data of individuals into novel biomarkers that can detect the decrease in motor-cognitive response due to the increase of cognitive load as individuals develop MCI or AD. Given the intrinsic ease of use and low cost of wearable sensors, their system has great potential to revolutionize the objective assessment of MCI and AD progression and are expected to reduce the health care cost by improving the monitoring of the older population and reducing the unnecessary frequent health care utilization and hospitalizations.

6. **Grant #9AZ06:** Effect of Neuronal Activity on Synaptopathy in Alzheimer's Disease using a Novel Multi-electrode Microfluidic Platform

**Principal Investigator:** Jianning Wei, PhD

**Organization:** Florida Atlantic University

**Abstract of Proposed Research:** Synaptic dysfunctions and synapse losses are considered among the earliest pathogenic events in Alzheimer's disease (AD). Identifying these pathological synaptic changes (synaptopathy) is thus crucial for revealing early interventions. Most efforts are directed to investigate how pathological proteins, beta-amyloid and hyperphosphorylated tau, affect synaptic functions. However, the role of neuronal activity on beta-amyloid and tau-mediated synaptic changes in AD remains largely unexplored. This is partially due to the lack of an appropriate platform to biochemically and spatiotemporally study synaptic changes at high resolutions. Conventional neuronal culture approaches have limited applications in selectively studying nerve terminals without affecting cell bodies. This aspect of study is crucial to understand how neuronal activity, which can be influenced by different environmental stimuli, modifies the progression of AD. Dr. Wei and associates have developed a novel in vitro microfluidic platform to study synaptic functions. Microfluidic chambers can provide unique insight into the axonal compartments independent of the soma and enable them to study the spatial role of beta-amyloid and Tau. The built-in microelectrodes in these chambers allows them to investigate AD-associated synaptic dysfunctions coupled with programmable neuronal stimulations. In this pilot proposal, they propose to use this novel platform to study how different patterns of neuronal activity (physiological vs. repeated stimulation) contribute to AD synaptopathy. While synaptopathy can be studied from different perspectives, they will focus on local protein degradation, which is spatiotemporally regulated by neuronal activity and remains largely unknown in AD pathology. The researchers hypothesize that protein turnover in response to repeated synaptic activity is impaired in AD, which further contributes to local protein aggregates formation, leading to synaptic dysfunctions and losses. To achieve this, they will use primary neuronal cultures obtained from postnatal day 1 (P1) 3x Tg-AD transgenic AD and wildtype pups. 3x Tg-AD transgenic mice are useful to study plaque and tangle pathology associated with synaptic dysfunctions. The following two aims are proposed: Aim 1: To investigate activity-dependent synaptic protein trafficking in AD primary neurons; Aim 2: To investigate activity-dependent synaptic protein turnover in AD primary neurons. A combination of molecular, genetic, biochemical approaches and live cell imaging will be used to analyze synaptic protein trafficking/distribution in different compartments of neurons (Aim 1) and monitor protein/organelle degradation at synaptic terminals (Aim 2) under programmable neuronal stimulation. Successful completion of these studies will provide new insights for activity-dependent synaptic changes at axonal terminals. The acquisition of such knowledge is critical to understand early molecular pathology of AD in the context of neuronal activity, which is complex and of high interest for AD research. The proposed study should present a valuable set of data to evaluate the promise of targeting synaptic function as a potential novel therapeutic strategy in AD treatments. This research is highly innovative for its interdisciplinary novel approaches that combine both biology and engineering expertise to spatiotemporally investigate synaptic stability at molecular levels in AD.

7. **Grant #9AZ07:** Shared Neuroanatomical Models of Psychiatric Conditions and Alzheimer's Disease Spectrum Disorders: The Effects of Depression, Anxiety, and Sleep Disturbance and Associated Changes in Brain Morphology Leading to Alzheimer's Disease.

**Principal Investigator:** Shanna L. Burke, MSW, MPH, PhD

**Organization:** Florida International University

**Abstract of Proposed Research:** Dr. Burke and her research team will examine the relationship between the presence of depression, anxiety, and sleep disturbance and regional changes in brain structure, examine the relationship between cognitive status and structural brain changes, and identify biomarkers of disease severity and stage shared by both psychiatric conditions and Alzheimer's disease (AD) and other dementias, while accounting for apolipoprotein e (ApoE) genotype. Emerging research provides evidence that psychiatric conditions increase risk for neurodegeneration. Neurodegeneration leads to AD and other dementias, and changes in brain structures can serve as biomarkers. The link between psychiatric conditions and AD and other dementias remains under study, but both cause changes in brain structure. It is hypothesized that the changes in brain morphology due to psychiatric conditions leads to subsequent neurodegeneration. This study will examine psychiatric conditions and associated subsequent neurodegeneration using shared biomarkers of disease severity and stage. There is an urgency to fully characterize regional brain changes resulting from psychiatric conditions, which often manifest prior to age 65, but may not exhibit a clinically observable neurodegenerative effect until later in life, often after age 65. ApoE e4 is a significant risk factor for AD and ApoE genotype also affects the risk for development of psychiatric conditions. ApoE e4 can interact with depression, anxiety, and sleep disturbance to increase the risk of mild cognitive impairment (MCI) and AD and will be accounted for in the shared biomarkers model, in addition to neuroimaging biomarkers. Three aims will organize this research investigation: Aim 1: To determine volumetric ranges of brain structures corresponding to those with depression, anxiety, and sleep disturbance, and whether the ranges vary from those without these conditions Aim 1a: To determine volumetric ranges of brain structures corresponding to those with normal cognition, MCI, dementia, and whether the ranges vary between these conditions Aim 1b: To determine volumetric ranges of brain structures associated with the six ApoE genotypes, and whether the ranges vary between the genotypes. Aim 1c: To determine at what point volumetric ranges of brain structures overlap between psychiatric conditions and cognitive statuses, while accounting for ApoE in order to identify shared neuroimaging biomarkers of disease severity and stage. Aim 2: To determine to what extent the change in brain structure, significantly affected by the psychiatric conditions of interest, predict a specific cognitive status Aim 3: To verify the predicted cognitive status using post-mortem neuropathological data Given that a third of older adults who are clinically asymptomatic may possess pathophysiological features of AD, including structural changes in brain regions, up to 20 years before observable symptoms appear, it is essential to understand how common psychiatric conditions, prevalent among 30-50 year-olds, influence brain morphology so early in the disease process. Understanding how common psychiatric conditions and subsequent changes in regional brain structure influences AD risk, while accounting for ApoE genotype, may provide a possible avenue for early intervention in a set of modifiable risk factors for AD and related dementias.

8. **Grant #9AZ08:** Identifying Functional Mutations in Top Alzheimer's Disease GWAS Genes using Long-read Sequencing in Brain Tissue

**Principal Investigator:** Mark T W Ebbert, PhD

**Organization:** Mayo Clinic Florida

**Abstract of Proposed Research:** Because of extensive efforts from large collaborative consortiums, such as the Alzheimer's Disease Genetics Consortium (ADGC) and the International Genomics of Alzheimer's Project (IGAP), there is a short list of top genes implicated in Alzheimer's disease, based on genome-wide association studies (GWAS). Unfortunately, there is currently lack some of the most crucial information necessary to understand how these genes either drive or modify disease development and progression: the functional mutations driving these GWAS signals. The large Alzheimer's Disease Sequencing Project (ADSP) is currently underway in an effort to identify small functional mutations. Dr. Ebbert and his team hypothesize, however, that many of the current GWAS signals are being driven by large structural mutations that are challenging to identify with conventional short-read sequencing approaches. Indeed, a repeat expansion in ATP-binding cassette subfamily A member 7 (ABCA7) associated with Alzheimer's disease was described in *Acta Neuropathologica*, earlier this year. Thus, they seek to perform deep, targeted long-read DNA sequencing and deep, targeted long-read RNA isoform sequencing (IsoSeq) in the lateral entorhinal cortex using PacBio long-read technology, which is best-suited for identifying structural mutations and accurately sequencing individual RNA isoforms. They believe their long-read sequencing efforts will compliment short-read sequencing efforts by the ADSP. They have been working with PacBio to develop and refine two independent targeted sequencing approaches over the past year, and have preliminary data demonstrating their ability to successfully apply them, including in Alzheimer's disease. The team recently published a paper in *Molecular Neurodegeneration* comparing how well the PacBio and Oxford Nanopore Technologies sequencing technologies can sequence through what may be the most challenging repeat expansion known: the ALS- and FTD-causing C9orf72 'GGGGCC' repeat expansion. They believe their approach provides a clear path to understanding a crucial aspect of Alzheimer's disease etiology by identifying structural mutations, including repeat expansions, that may be the functional mutations associated with GWAS hits researchers have been looking for. Their approach will also enable them to identify aberrant RNA isoforms that drive disease development and progression. By studying the lateral entorhinal cortex, where pathogenesis typically begins, they can maximize the likelihood of finding any mutations involved in disease, ultimately leading to effective therapeutics. It is critical that they study these mutations in the diseased tissue, to measure DNA and RNA modifications where disease occurs. They have assembled a strong team, including Dr. Dennis Dickson, a renowned neuropathologist, Dr. Mark Ebbert, a successful Alzheimer's disease geneticist, bioinformatician, and computational biologist, and Tanner Jensen, a talented bioinformatician in Dr. Ebbert's lab. They also have collaborators at Brigham Young University (BYU), Integrated DNA Technologies (IDT) and Pacific Biosciences (PacBio), with whom they have refined the targeted approaches. They are confident that existing evidence and their preliminary data support their aims, and that this project will advance Alzheimer's disease research.

9. **Grant #9AZ09:** Therapeutic Roles of Surrogate Wnt Agonist in Alzheimer Disease

**Principal Investigator:** Yonghe Li, PhD

**Organization:** Mayo Clinic Florida

**Abstract of Proposed Research:** Wnt proteins are a large family of secreted glycoproteins that bind to a cell surface receptor complex and subsequently activate the

Wnt/ $\beta$ -catenin signaling pathway. Wnt/ $\beta$ -catenin signaling is an essential pathway that regulates numerous cellular processes, including cell survival. The ultimate goal of the current project is to develop novel specific Wnt activators for Alzheimer's disease (AD) therapy. AD chronically leads to dramatic neuronal loss, as they undergo apoptotic cell death, a direct consequence of the  $\beta$ -amyloid deposition and tau protein hyperphosphorylation, which are two major hallmarks of AD. It is well established that Wnt/ $\beta$ -catenin signaling not only inhibits A $\beta$  production and tau phosphorylation, but also enhances synaptic plasticity, which is one of the important neurochemical foundations of learning and memory. Moreover, Wnt/ $\beta$ -catenin signaling is a key positive regulator of neuronal survival and adult neurogenesis in brain. Wnt/ $\beta$ -catenin signaling is greatly suppressed in AD brain, and deregulated Wnt/ $\beta$ -catenin signaling plays an important role in the pathogenesis of AD. Therefore, Dr. Li and associates hypothesize that activation of Wnt/ $\beta$ -catenin signaling represents an opportunity for rational AD therapy. Although the therapeutic potential of Wnt proteins has long been recognized, challenges associated with the hydrophobic nature of these proteins preclude their *in vivo* use. Recently, their collaborator Dr. K. Christopher Garcia at Stanford University School of Medicine developed a water soluble surrogate Wnt agonist (scFv-DKK1c). This easily produced, non-lipidated Wnt surrogate agonist can specifically activate Wnt/ $\beta$ -catenin signaling both *in vitro* and *in vivo* (Janda et al., *Nature*, 545:234-237, 2017). Moreover, Dr. Garcia's lab very recently optimized scFv-DKK1c and developed a next generation surrogate (NGS). In their preliminary studies, they found that NGS can activate Wnt/ $\beta$ -catenin signaling at the concentration as low as 1 nM in induced pluripotent stem cell (iPSC)-derived human neurons. They herein proposed a collaborative effort to determine therapeutic roles of NGS in AD. Therefore, NGS will be evaluated on Wnt activation, A $\beta$  production, tau phosphorylation, neuronal survival, and synaptic plasticity in iPSC derived human neurons carrying ApoE  $\epsilon$ 4/ $\epsilon$ 4. ApoE  $\epsilon$ 4 is the strongest genetic risk factor for late-onset AD. Moreover, NGS will be examined in the 5xFAD mouse AD model to explore its anti-AD efficacy *in vivo*. Successful completion of current study will allow them to identify the surrogate Wnt agonist as a promising candidate for a novel therapeutic application to AD.

10. **Grant #9AZ10:** Validation of Novel, Selective Autophagy Biomarkers in Alzheimer Disease

**Principal Investigator:** Wolfdieter Springer, PhD

**Organization:** Mayo Clinic Florida

**Abstract of Proposed Research:** Alzheimer disease (AD) is the most common neurodegenerative disorder affecting more than 5 million individuals in the US with close to 500,000 in Florida alone. Clinically, AD is characterized by severe cognitive, behavioral, and motor impairments resulting from progressive synaptic dysfunctions and neuronal loss. Neuropathologically, AD is defined by the formation of insoluble protein aggregates including extracellular amyloid- $\beta$  (A $\beta$ ) plaques and intracellular tau tangles. In addition to these late-stage hallmarks, mitochondrial dysfunctions and impairments of the autophagy-lysosome system are well documented early signs of AD. Mitochondria (the cellular power houses), autophagy (the cellular garbage collection) and lysosomes (the cellular waste disposal and recycling system) are dynamic and vital organelles that are particularly important in neurons for their development, function, and survival. Emerging findings suggest an intimate interrelationship between them and it is now evident that dysfunctions in either organelle results in impairment of the others. Those

dysfunctions not only prominently occur in the prodromal phase of AD, but also further promote the accumulation of A $\beta$  and tau through increase in oxidative damage, cellular energy deficits and progressive failure of cellular degradation. To prevent accumulation of damaged organelles and proteins, cells employ several pathways of general and selective autophagy such as mitophagy (clearance of failing or worn out mitochondria), aggrephagy (clearance of protein aggregates), and secretory autophagy (release of intracellular material to the outside). Individual forms of selective autophagy are regulated through combinations of post-translational modifications that are typically transient unless flux through the clearance arms is impaired. These specialized modifications not only label the respective cargo (such as the mitophagy tag phosphorylated ubiquitin), but also modify the autophagy receptors (such as p62/SQSTM1) that decode the signals and facilitate routing of material within the autophagy-lysosome system. Dr. Springer's lab capitalized on these findings and quantified levels and distribution of those selective autophagy markers in larger cohorts of human post-mortem brain samples from AD patients. Compared to controls, they found significant increases of distinct autophagy labels and receptors that correlated with the respective neuropathologies. In addition to immunohistochemical analyses they developed highly sensitive ELISA-type assays on a Mesoscale discovery platform and confirmed the utility of these markers as quantitative measures of mitochondrial damage, protein aggregation and/or impairments of selective forms of autophagy. Here they aim to validate their potential as a biomarker (panel) in blood and cerebrospinal fluid (CSF) samples from AD patients. They will leverage existing collections of these body fluids to correlate selective autophagy with the progression of disease from mild cognitive impairment to dementia. As a result, their study will not only evaluate novel biomarkers (Focus Area 2.4) but may also help define mechanisms of neurodegeneration (Focus Area 2.2) and provide novel therapeutic targets and strategies for AD (Focus Area 2.1).

11. **Grant #9AZ11:** Impact of the MindSight Training Program on Patients with MCI and Early Stage Dementia

**Principal Investigator:** Maria T Greig-Custo, MD

**Organization:** Mount Sinai Medical Center

**Abstract of Proposed Research:** The goal of the MindSight Training Program is to improve functional learning capacity, and quality of life among patients with MCI and Early Stage Dementia, through a Randomized control trial. The MindSight training program incorporates a dyad approach (i.e., the cognitively impaired participant and a partner). The role of the partner is to reinforce all the techniques learnt at each weekly MindSight session. The program is designed to be used in small groups in a classroom format where participants will learn exercises that may help maintain function and develop strategies to help reduce emotional stress, while increasing optimal usage of the cognitive skills they currently possess. Participants will be learning to use several different mind-body approaches, cognitive behavioral skills, spaced retrieval, procedural memory, focused attention, associations, and other techniques that engage cognitive functions while simultaneously practicing daily stress reduction coping skills. The proposed project is an extension of the MindSight Pilot Grant (awarded by this funding body, in 2016-17), which has established the feasibility of recruiting and retaining dyads for a six-week course and conducting pre and post cognitive testing. This six-week program (one session per week) will recruit dyads from patients attending the Wien Center Clinic, and from those enrolled in their Alzheimer's Disease Research Center.

Dyads will be randomly allocated into: (1) a group that receives a combination of Mindfulness Training and Cognitive Teaching Techniques, versus (2) a Social Interaction Control Group that engages in informal discussion of methods for cognitive enhancement and stress reduction (such as learning a new language, acquiring a new hobby, joining a book club, doing yoga and tai chi, joining a gym). Before and after the six-week course patients will have: (a) a 90 minute comprehensive test battery, (b) questionnaires on general well-being and quality of life, basic and instrumental ADLs (i.e., functionality), and (c) salivary biomarkers of stress and inflammation (cortisol, alpha-amylase and C-Reactive Protein), which will serve as the outcome measures of the study. The current version of MindSight incorporates Mindfulness as a coping approach that provides resources and support for patients and their partners who struggle with the fear and stress commonly experienced with MCI and AD. The purpose of the MindSight program is to allow patients to maintain or prolong independence, sense of well-being and functionality and improve self-confidence in communication. It is expected that the study partners of the participants will also benefit from this training program by improving their quality of life and of the patients and thereby reduce their levels of stress. The proposed project is very much aligned with the goals of the Florida Department of Elder Affairs, Alzheimer's Disease Initiative and its Dementia Care and Cure Initiative. The results of this study will provide critical data that will provide methods to enhance clinical interventions for MCI/AD patients and their partner and will provide necessary preliminary data for a future large scale, NIH funded, clinical investigation.

12. **Grant #9AZ12:** The Florida REACH Translation Project: Translating an EBP for an Outpatient Clinical Setting to Reach Diverse Community Members

**Principal Investigator:** Tracy Wharton, PhD, MSc, MEd, MSW, LCSW

**Organization:** University of Central Florida

**Abstract of Proposed Research:** The REACH II intervention is the gold-standard for evidence-based practices that address burden, stress, and positive aspects of caregiving. Unfortunately, despite over 200 existing intervention models, few have been successfully translated in a sustainable way into community-based settings. One potential for sustainability of such a translation is to embed it into an outpatient clinical setting. Establishing feasibility and positive outcomes in such a translation would offer new possibilities for reaching families living with Alzheimer's disease & other dementias (ADOD). This pilot study translates the REACH II intervention to be provided by behavioral health team members in a specialty outpatient clinic connected to one of the MDCs. There are distinct benefits of approaching intervention through outpatient connection. Although huge swaths of Florida are ethnically, racially, and linguistically diverse, there is disparity among families that engage with existing education and training programs. In addition to racial/ethnic diversity, families who repeatedly return to the clinic in crisis tend to be less wealthy than their counterparts, less aware of regional resources that may be available and less inclined to use them. This pilot program involves applied research into a novel approach that provides access to anyone who comes to the clinic for diagnosis, with a program that builds a bridge between the medical team and the psychosocial intervention, capitalizing on the rapport and trust that is built with the team, and providing in-house opportunities to engage diverse populations with a program grounded strongly in the evidence base. Goals of the program include: increasing access to acute healthcare advice and services connected to patient care teams, lowering caregiver burden, supporting quality of life and mental

health for both partners, and teaching transferable skills prior to crisis. By providing early education and training for families, the ultimate goal is to offer person-centered practices and non-pharmacological approaches that can be used to address a range of behavioral expressions and other challenges over the course of the disease, leading to lower service utilization, improved quality of life, and continuity of care for the individual and their family. This pilot will involve training staff of the MDC and graduate students to provide the intervention. Training will be provided by Drs. Wharton and Paulson. The intervention will be integrated into the specialty outpatient clinic, supervised in practice by the clinical team: social worker Judy Clark, nurse specialist Gayle Shepherd, and geriatrician Dr. Rosemary Laird, bridging the gap between medical and social needs. Patients and their families who are given a diagnosis at the clinic will be referred to begin the REACH intervention in the next two weeks. Families will have a total of 4 in person meetings at the clinic and two therapeutic phone calls. The intervention focuses on: education around ADOD, safety, planning for the future and connecting medical and psychosocial support, behavioral expressions, self-care, grief, and family coping styles. Validated assessment tools will be used to collect data regarding caregiver mental health, dementia-related behaviors and risks in the home, along with participant satisfaction and a fidelity tracking form.

13. **Grant #9AZ13: Is Cortisol Really a Factor in Cognitive Decline?**

**Principal Investigator:** Cynthia Garvan, PhD

**Organization:** University of Florida

**Abstract of Proposed Research:** Increased cortisol levels have been reported in patients with Alzheimer's disease (AD), and significant preclinical data have demonstrated that hypothalamic-pituitary-adrenal (HPA) axis activation exacerbates amyloid- $\beta$  deposition and tau phosphorylation in the brains of AD-relevant mouse models. Evidence from recent studies suggest that HPA axis dysregulation can precede the diagnosis of AD by up to 6 years and may accelerate disease progression and cognitive decline. At this point, it is not known whether brain exposure to high cortisol concentrations is a factor in the development of AD, and historically the measurement of long-term cortisol exposure in AD patients has been difficult due to the majority of studies relying on acute measurements of plasma cortisol. There is a critical need for noninvasive and accurate measures of long-term average cortisol levels to advance the understanding of HPA activation along the course of AD development, and to further elucidate the potential of cortisol to serve as a biomarker of AD risk and/or AD progression. Measurement of hair cortisol levels has recently gained attention as a reliable measure of long term cortisol exposure. Dr Garvan's team will be able to use a novel method of hair cortisol measurement developed at the University of Florida to overcome the difficulties of ascertaining chronic cortisol exposure that have been encountered in previous studies of HPA axis dysregulation along the course of AD progression. They propose to collect hair samples from among 346 individuals who are participants at the 1Florida Alzheimer's Disease Research Center (ADRC). In this cohort the consensus diagnoses are: cognitively healthy (n=33), pre-mild cognitive impairment (n=37), early mild cognitive impairment (eMCI) (n=67), late early mild cognitive impairment (LMCI) (n=35), and dementia (n=54). PET scans for amyloid- $\beta$  deposition have confirmed that the impairment or dementia in 115 of these patients is due to AD. With the cortisol measures in addition to the amyloid PET scan data, they will be able to: 1) validate findings in recent studies which have shown a relationship

between cortisol levels and stages of cognitive decline, 2) evaluate if cortisol levels are associated with rate of cognitive decline, 3) determine the potential of cortisol level to serve as an early biomarker of AD risk, and 4) garner preliminary data for a planned longitudinal study of the role of cortisol in AD risk and AD progression. Their proposed project is aligned with the Ed and Ethel Moore Alzheimer's Disease Research Program's Priority Area 3, specifically with Focus Area 3.1, Risk factors for cognitive decline.

14. **Grant #9AZ14:** Utilizing Data from the Electronic Medical Record to Predict Alzheimer's and Dementia Risk

**Principal Investigator:** Demetrius M Maraganore, MD

**Organization:** University of Florida

**Abstract of Proposed Research:** Alzheimer disease (AD) is the 6th leading cause of death in the United States and presents a substantial burden to affected individuals, their families, and healthcare systems. Today more than 5.7 million Americans are living with AD and the prevalence is expected to reach up to 14 million by 2050. Decades of clinical trials of treatments for AD have ended in failure, but the literature supporting the presence of risk factors continues to grow. Risk factors that are well supported in the literature include many factors that are routinely captured in commercial electronic medical records (EMRs), including obesity, hypertension, high cholesterol, sleep disorders, anxiety disorders, depression, concussion, early menopause, inflammatory/infectious conditions (e.g. periodontitis), heart problems, diabetes, family history, alcohol use, smoking habits, exercise habits, and more. A growing body of evidence suggests that AD processes begin in the brain during midlife and that interventions during the latency of disease progression may lead to improvement in cognition, delay of symptoms, or prevention of disease (primary prevention). As such, Dr. Maraganore and associates seek to determine which patients are at high risk of AD before they begin to develop symptoms to allow for intervention. Using historical data collected at primary care provider (PCP) visits and stored in the EMR's relational database, they seek to build an algorithm to identify a patient's risk for dementia and AD, to prioritize patients that may benefit from brain health interventions (primary prevention strategies). They will utilize historical data electronically captured by the commercial EMR (Epic Systems) at the University of Florida in Gainesville, to develop a dementia/AD prediction model. They will then seek to replicate the model using historical data electronically captured by the commercial EMR (Epic, other commercial EMR platforms) at other practices participating in the OneFlorida Clinical Research Consortium (<http://onefloridaconsortium.org>). If the AD prediction model is replicated, they will then build into the commercial EMR at the University of Florida clinical decision support tools to identify patients at highest risk for dementia, and to guide their referral by PCPs to the University of Florida's Brain Health Clinic (directed by the Principal Investigator). They will also share the AD prediction model algorithm and clinical decision support tools with other OneFlorida practices. This study will build on work that the Principal Investigator conducted previously at NorthShore University HealthSystem in Evanston, IL, where a preliminary dementia/AD prediction model using the EMR was piloted. However, the NorthShore model did not incorporate new medical diagnostic codes (ICD-9 based only), and it was not independently replicated or implemented into clinical practice. It was also restricted to people ages 60 and older. The refined model developed through this proposal will determine the likelihood of a

Floridian ages 50 and older to develop dementia or AD over five years. The long-term goal is to establish in Florida a state wide, EMR-based primary prevention initiative to reduce the incidence of AD; Florida is otherwise expected to have the highest prevalence of AD per capita of all 50 states for decades to come.

15. **Grant #9AZ15:** Association of PET Amyloid Status with Cognitive and Functional Outcomes of Behavioral Interventions in Mild Cognitive Impairment

**Principal Investigator:** Glenn Smith, PhD

**Organization:** University of Florida

**Abstract of Proposed Research:** The overarching goal of the proposed project is to increase understanding of the mechanisms underlying outcomes following cognitive training or physical exercise interventions in people with mild cognitive impairment (pwMCI). Accumulating evidence from healthy samples indicates that cognitive training (CT) and physical exercise (PE) can restore or strengthen specific cognitive and functional abilities, e.g., aide cognitive reserve. However, results from clinical trials are inconclusive as to whether cognitive training and physical exercise are effective interventions for delaying or slowing decline in MCI. But previous studies have not accounted for the influence of the underlying neuropathology on improvements or lack thereof in outcomes following CT and PE interventions. It has been proposed that CT and other lifestyle factors may serve as neuroprotective factors in healthy samples but that as the disease progresses (i.e., MCI emerges) the mechanisms underlying the influence of these factors may switch to being compensatory. What has not been clearly investigated in MCI behavioral trials is whether elevated levels of amyloid-beta ( $A\beta$ ), a hallmark biomarker of Alzheimer's disease (AD), specifically alters the impact of CT and PE on cognitive and functional outcomes (e.g., memory, instrumental activities of daily living). Roughly 60% of MCI individuals are thought to display pathological levels of  $A\beta$  on amyloid PET scanning. Thus, not all those with an MCI diagnosis have significant  $A\beta$  burden. Rather other non-AD etiologies including cerebrovascular disease and even mood disturbance may account for the presentation of MCI. The aims of the present study are to characterize how the efficacy of CT and PE interventions in individuals with MCI associate with  $A\beta$ -positive versus  $A\beta$ -negative status. Because amyloid scanning is very expensive, Dr. Smith and associates will examine this association in a cost-effective manner by utilizing participants who are in a behavioral trial of CT vs PE vs active control that is approaching completion. The Physical Exercise And Cognitive Engagement Outcomes for Mild Neurocognitive Disorder (PEACEOFMND) trial is following out to six months, 60 pwMCI who were randomized to computerized cognitive training or physical exercise or a wellness education active control. They will re-engage these participants, obtain their cognitive and functional outcomes at 18 months post intervention. They will then partition the 60 pwMCI into tertiles based on Everyday Cognition scale outcomes and obtain PET scans from those in the highest and lowest tertiles. Doing so will reduce PET scanning costs by one-third while maintaining the statistical power to detect medium to large effect. Their working hypothesis is that those with the best outcomes will be far less likely to be  $A\beta$ -positive than those with the worst outcomes. They will also engage in exploratory analyses to see if  $A\beta$  status adds predictive power beyond baseline hippocampal volume. If their predictions are met, the findings may have important implications for identifying subgroups of individuals with MCI who will likely benefit most

from CT. The indirect impact of this study may also better direct public health care spending.

16. **Grant #9AZ16:** The Two Faces of Hypoxia in Alzheimer's Disease

**Principal Investigator:** Gordon Mitchell, PhD

**Organization:** University of Florida

**Abstract of Proposed Research:** Sleep apnea is associated with repeated periods oxygen reduction (intermittent hypoxia) and disturbed sleep. The risk of developing sleep apnea in adults increases with age and considerable evidence supports a role of sleep apnea in the development of cardiovascular disease, metabolic syndrome and cognitive impairment. Since age is also a major risk factor for Alzheimer's disease (AD), it is not surprising that both sleep apnea and AD are often found in the same individual. The co-occurrence of sleep apnea with Alzheimer's disease is not just an unfortunate coincidence; indeed, AD may cause sleep apnea, and, in turn, sleep apnea may accelerate AD progression. Most studies concerning the harmful effects of sleep apnea on the progression of AD concern the impact of chronic intermittent hypoxia (CIH) on amyloid beta, a protein that forms sticky clumps between brain cells. However, it is not known if CIH similar to that experienced during sleep apnea can exacerbate clustering of tau protein into a tangled mess (tau tangles), which is linked to loss of neurons. Formation of tau tangles and neuronal death are critical events in human AD and in a mouse model used in AD research, the rTg4510 mouse. Although the severe CIH associated with sleep apnea may increase AD risk, less severe (‘low dose’) protocols of intermittent hypoxia are known to increase growth factors that elicit neuroplasticity and promote neuron survival (without eliciting pathology); such ‘low dose’ protocols are often referred to as repetitive acute intermittent hypoxia (rAIH). Since rAIH preconditioning may enhance cognitive function in normal individuals, it could have beneficial effects, minimizing tau tangle formation, neuronal death and/or AD progression. Understanding the differential effects of ‘high dose’ versus ‘low dose’ intermittent hypoxia on critical disease events in AD, such as tau tangle formation, will help determine how sleep apnea increases the risk for AD and if low levels of intermittent hypoxia exposure could actually reduce the risk of developing Alzheimer's Disease.

17. **Grant #9AZ17:** Mechanisms of Abnormal Neuronal Tau Accumulation, Interactions with Amyloid-beta and Pathological Sequelae.

**Principal Investigator:** Benoit Giasson, PhD

**Organization:** University of Florida

**Abstract of Proposed Research:** The presence of brain extracellular deposits of amyloid-beta peptides and the accumulation of neuronal aggregates comprised of the protein tau are defining hallmarks of Alzheimer's disease (AD). The abundance and distribution of tau aggregates correlates with disease progression and clinical symptoms in AD. The direct involvement of tau in disease has been unequivocally established by the discovery of tau mutations that results in progressive dementia. However, the mechanisms that lead to abnormal tau accumulation and whether pathogenic interaction between amyloid-beta peptides and tau lead to AD type neurodegeneration still remain

unclear. Although tau is normally more abundant in the distal (axon) compartment of neurons, in AD it abnormally accumulates in the proximal compartments (cell body and dendrites). Numerous tau mutations that cause neurodegeneration affects tau's ability to interact with microtubules, a key component for its transport to neuronal distal component. Until recently, tau mutations were reported to only reduce its interaction with microtubules, but new mutations have been identified that demonstrated the opposite property. In this project Dr. Giasson and associates propose to investigate the hypothesis that alterations in tau structure, resulting from either mutations or a unique series of tau modifications that is a known marker of early AD tau pathology, can lead to abnormal tau compartmentalization and this process can be exacerbated by amyloid-beta deposition promoting neurodegeneration in rodent models of AD. Collectively, these studies will provide novel insights in the molecular and cellular mechanisms influencing the aberrant accumulation of AD protein deposits and the pathogenic consequences associated with tau aggregation with therapeutic implications.

18. **Grant #9AZ18:** Responses to a Standardized Approach to Advance Care Planning in Cognitive Disorders Clinic

**Principal Investigator:** Neal J. Weisbrod, MD

**Organization:** University of Florida

**Abstract of Proposed Research:** Advance care planning in Alzheimer disease and other forms of dementia poses unique challenges to clinicians. The insidious deterioration in cognitive faculties encourages the assumption that there will be a better time to address those difficult conversations later down the road. Additionally, as clinicians worry that having discussions about bad outcomes or death will damage their relationship with their patient and their family, or cause undo anxiety or sadness if not timed properly. Unfortunately, this combination of forces often results in advance care planning being addressed after dementia has progressed and requires a surrogate decision maker. It may only come up for the first time during a critical illness. To improve advance care planning in patients with Alzheimer disease and other cognitive disorders Dr. Weisbrod suggests a routine and stepwise approach to addressing these conversations in the clinic, addressing priority area 1.3.1 (Advance Care Planning) from the Ed and Ethel Moore Alzheimer's Disease Research Program Funding Opportunity Announcement. For all new patients they aim to explore devoting the 3rd clinic appointment to advance care planning. For, any patient diagnosed with mild cognitive impairment (MCI) by the 3rd appointment the conversation will revolve around exploration of values and beliefs and assignment of a surrogate decision maker. An advance directive form will be introduced to the patient and family and they will be encouraged to discuss and complete it. For a patient diagnosed with early dementia, further attempts will be made to complete the advance care directive and additionally they will assess patient/surrogate preferences regarding code status using a physician orders for life sustaining treatment (POLST) form. For patients with moderate or severe dementia, they will further encourage completion of the AD and POLST forms and discuss patient/surrogate end-of-life values and preferences including their views on comfort-oriented treatment and hospice. To assess the outcome of this protocol they will measure the rate of entry of advance care planning information into the electronic health record (EHR). Additionally, the research team will survey the patients and family members who participated in the discussion in the office to evaluate their emotional and cognitive response to the conversation. They hope this pilot study will be helpful in

multiple ways. If a routine and standardized approach to advance care planning is met with positive reception by patients and family, it would alleviate clinician concerns that having this discussion will damage their patient-provider relationship. Additionally, this protocol could serve as a guide for providers unsure of what depth of advance care planning is appropriate for a specific patient. If poorly received by patients/families, this information would prime further work in applying a more delicate approach to advance care planning in this patient population.

19. **Grant #9AZ19:** Impact of Total Knee Replacement Surgery on Trajectory of Cognitive Decline in Individuals with Mild Cognitive Impairment (MCI)

**Principal Investigator:** Catherine Price, PhD

**Organization:** University of Florida

**Abstract of Proposed Research:** Older adults are at increased risk for cognitive decline following major surgeries with this having implication for neurodegenerative acceleration as well as post-operative and long-term care costs. Orthopedic replacement surgeries such as total knee replacement surgery have the highest rates of cognitive decline in older adults. This is alarming, for older adults are increasingly seeking joint replacement to reduce associated osteoarthritis pain and increase activity (i.e., quality of life). Unfortunately, at present there are no known surgical or anesthetic mechanisms for post-operative cognitive dysfunction. Rather, baseline cognition is the biggest risk factor for outcome. In Dr. Price's recent study following patients age 65 and older through knee replacement surgery with general anesthesia using the same surgeon and anesthesia protocol shows that patients with mild cognitive impairment (MCI) have: 1) significant decreases in brain communication (functional network connectivity) acutely after surgery (Huang, Tanner...Ding, Price, 2018; Hardcastle, Huang,...Ding, Price, 2018), 2) less microstructural free water change acutely after surgery, suggesting preoperative brain integrity is an important contributor to a normal reactive response (Tanner, Amin,...Mareci, Price, in review); and 3) greater intraoperative frontal EEG variability from time of tourniquet up to tourniquet down, suggesting desynchronization of neuronal networks with implications for cognitive insult (Hernaiz...Price, in review). These findings bring follow-up questions. Why are patients with MCI's brains vulnerable to surgery and anesthesia? Should MCI patients have different anesthetic approach? Are MCI patients who show acute brain changes after surgery more likely to have neuronal change even after one year? These are important questions that require investigation with longitudinal imaging and strategic focus on MCI recruitment. Dr. Price and associates seek funding to address these important questions with the data acquired rapidly over a period of two years. The study methodology will involve a prospective recruitment of individuals electing total knee replacement and randomized to general anesthesia (n=14) versus regional anesthesia (n=14). Both groups will acquire baseline MRI using sophisticated structural, functional, and diffusion sequences and complete cognitive testing at a pre-surgery/baseline time point followed by repeat testing at three weeks, three-months, and one-year post-operative/post-baseline. Participants will also acquire a repeat MRI 48 hours after their baseline scan to identify acute functional/structural changes and rule out embolic stroke. A subset of patients (total n=14) with and without characteristics of mild cognitive impairment (MCI) will complete baseline and repeat MRIs. The study design will consider contributing variables (intraoperative EEG intraindividual variability, sleep, pain, delirium, and post-operative activity level) on MRI and cognitive/functional

outcome. The study's findings will bring them closer to understanding neural mechanisms for cognitive change after surgery and accelerate large scale investigations addressing perioperative interventions for patients with MCI/AD.

20. **Grant #9AZ20:** Role of Gut Microbiota on the Brain Metabolism, Cognition, Immune Function and Inflammation in Alzheimer's Disease: Novel Biomarkers and Understanding Mechanisms

**Principal Investigator:** Varan Govind, PhD

**Organization:** University of Miami

**Abstract of Proposed Research:** Despite identification of the hallmark pathological features of Alzheimer's disease (AD), which include extracellular amyloid beta plaques and intracellular tau neurofibrillary tangles in the brain, the underlying causes and mechanisms contributing to these features remain largely unknown. Thus, the quest to identify the source of AD pathology keeps on expanding. Since the brain and the gut are interconnected through the gut-brain axis, alterations in the diversity and composition of gut microbiome (bacteria, fungi, viruses, etc.; aka gut microbiome dysbiosis) may modulate metabolic and physiological functions of the central nervous system (CNS) that includes the brain and spinal cord, thereby causing or contributing to pathogenesis in the CNS. Most recently, dysbiosis of the gut microbiota has been shown to play a role in the pathogenesis of AD and other neurodegenerative diseases. Furthermore, healthy gut microbiota or its metabolic products are necessary for the maturation, activation and optimal functioning of microglia, which are the resident macrophage cells that is responsible for scavenging plaques and infectious agents in the CNS. Thus, it is possible that dysbiosis of the gut microbiota itself will compromise the functioning of microglia (the active immune system) in the CNS. Findings from several preliminary investigations indicated that the mechanisms contributing to the development of AD pathology may involve gut microbiota-derived metabolites (e.g., gamma amino butyric acid; amyloid beta proteins and lipopolysaccharides); leaky guts; immune-modulating mediators and inflammation. However, to the best of Dr. Govind's knowledge, there is no published comprehensive data that examined associations between dysbiosis of the gut microbiome, concentration of brain GABA (chemical messenger), markers of brain inflammation (myoinositol and free water fraction), peripheral amyloid beta protein concentrations, markers of peripheral inflammation and immune function, and measures of neurocognitive function in patients with AD. The goal of this study is, therefore, to test the associations between dysbiosis of the gut microbiome (i.e., diversity and composition) and intestinal permeability and microbial translocation markers with brain GABA, brain inflammation markers (myo-inositol and choline-containing compounds (Cho); free water content), peripheral amyloids and lipopolysaccharides, peripheral inflammation markers and cognitive function in patients at the early stage of cognitive impairment and age-matched healthy controls. The specific aims include 1) Compare the diversity and composition of gut microbial communities of stool samples from patients with cognitive impairment and healthy control using 16S rRNA-based metagenomics. Hypothesis: The AD group will have a different microbiota diversity and composition than controls. 2) Correlate gut microbial dysbiosis measures with severity of disease using blood-based peripheral measures (amyloid peptides, lipopolysaccharides, inflammation), MRI-technique-based CNS measures (GABA, myo-inositol, Cho, free water content) and measures of neurocognition. Hypothesis: The gut microbial dysbiosis measures in AD group will have correlations with peripheral, CNS and neurocognition measures and

disease severity. The data obtained in this pilot study will enable them to identify novel biomarkers of AD risk and derive stable estimates of their variability across subjects for writing a standard grant application.

21. **Grant #9AZ21:** Postdoctoral Research Fellowship in Neuropsychology

**Principal Investigator:** Rosie E. Curiel, PsyD

**Organization:** University of Miami

**Abstract of Proposed Research:** The Center for Cognitive Neuroscience and Aging (CNSA; formerly known as the Center on Aging), has a robust and growing program of state and federally funded research devoted to developing novel diagnostic assessment paradigms and tools to detect preclinical Alzheimer's disease (AD) and related disorders. Moreover, the CNSA is home to the state-funded University of Miami Memory Disorders Clinic, and their clinician-scientists are active co-investigators on several AD-related projects including the 1Florida Alzheimer's Disease Research Center. This rich training environment has served as the platform upon which Dr. Curiel and associates have successfully and continuously trained Ed and Ethel Moore Postdoctoral Research Fellows since the program was initiated during the 2015-2016 year. The focus of the research fellowship is to offer a promising postdoctoral candidate the opportunity to receive specialty training in Alzheimer's disease by: a) developing enhanced clinical evaluation and diagnostic skills, b) participating in ongoing clinical research projects that are studying promising new methodologies to improve the clinical assessment of diverse older adults at risk for the development of AD and related disorders c) learning about cross-cultural neuropsychological assessment and the development of culturally fair diagnostic assessment instruments, which is of critical relevance in the State of Florida and d) receiving training in writing federally funded grant applications to prepare him/her to become an independent investigator. Competent clinical assessment that is sensitive to detect preclinical AD remains a critical priority area in Alzheimer's disease research. Offering this training opportunity to a neuropsychologist is of particularly high impact, in that this discipline plays a direct and critical role in Alzheimer's disease clinical research. In addition, the longitudinal nature of their research program will offer the unique opportunity for the fellow to assist with longitudinal data analysis, expose them to state-of-the-art cognitive assessment methods and various biological markers of AD pathology including amyloid and tau neuroimaging and cerebrospinal fluid markers. Drs. Rosie Curiel Cid and David Loewenstein, would serve as primary and secondary mentors, respectively. Together, they have two active longitudinal RO1 studies (Loewenstein-PI and Curiel-PI) funded by the National Institute on Aging, three active Ed and Ethel Moore AD research studies. In addition, Dr. Curiel Cid is a co-investigator for the University of Miami state-funded Memory Disorders Clinic and a major scientific project at the 1Florida ADRC, while Dr. Loewenstein co-leads the ADRC clinical core. This focused and highly productive program of research at the CNSA, along with the mentors' longstanding background in training post-doctoral fellows, offers an unparalleled specialty training opportunity for the postdoctoral candidate to expand their competency to serve older adults who are at risk for the development of neurodegenerative conditions such as AD.

22. **Grant #9AZ22:** Postdoctoral Fellowship in Cognitive Neuroscience and Neuropsychology

**Principal Investigator:** Philip Harvey, PhD

**Organization:** University of Miami

**Abstract of Proposed Research:** With the nation's aging population, maintaining cognitive health and functional independence among older adults is a key priority. There is promising data emerging regarding the effectiveness of targeted cognitive training interventions to improve the cognitive skills of older adults, which is essential to independent living. Dr. Harvey and the group of investigators at the Center for Cognitive Neuroscience and Aging (CNSA) have expertise in the early detection of cognitive change in persons at-risk for the development of neurodegenerative disorders as well as functional skills training and have developed real-world functional task simulations. Thus, the mentoring team is well poised to not only detect preclinical stages of dementia, but also to develop and deliver cognitive training interventions with the aim of promoting the maintenance of real-world functions among older adults representing diverse ethnic/cultural groups. The proposed one-year postdoctoral research fellowship will offer an individual with a postdoctoral degree in neuropsychology or cognitive neuroscience the opportunity to receive specialty training in Alzheimer's disease and related disorders. This fellowship will especially emphasize the development of cognitive interventions that can be piloted in their large and growing clinical research program in aging and cognition at the CNSA. The fellow will be exposed to the development and refinement of promising new clinical assessment methodologies, learn about and develop paradigms for cognitive interventions, receive training in research design and methodology, data analyses and learn to write federally funded grant applications to prepare him/her to become an independent investigator. The mentorship team has a longstanding history of training postdoctoral fellows. Dr. Philip Harvey (a former Ed and Ethel Moore Fellowship Mentor) would serve as the primary mentor given his expertise in the development and delivery of functional skills training and the neurosciences. Drs. Rosie Curiel Cid and David Loewenstein, would serve as secondary mentors. Together, Drs. Harvey, Curiel Cid and Lowenstein have three active longitudinal RO1 studies funded by the National Institute on Aging, and several active Ed and Ethel Moore AD research studies, which will serve as the training platform for the postdoctoral candidate.

23. **Grant #9AZ23:** Impacts of Neighborhood Greenness & Greening Initiatives on Alzheimer's Disease in Medicare Beneficiaries

**Principal Investigator:** Scott C. Brown, PhD

**Organization:** University of Miami

**Abstract of Proposed Research:** Dr. Brown and his team propose to expand the knowledge base relative to Alzheimer's disease (AD) prevention by investigating neighborhood greenness, a novel environmental risk/protective factor for AD. In prior research, they found that higher neighborhood block-level greenness --tree canopy and green space-- was associated with lower rates of AD in ~250,000 Miami-Dade County Medicare beneficiaries. The greenness to AD relationships were strongest in low-income neighborhoods, where the odds of AD were ~30% lower for individuals living on a high-greenness block compared to those living on a low-greenness block (1,2). Since they completed their 2010 study, Miami-Dade County planted >200,000 trees, focusing on low-income neighborhoods, achieving a countywide tree-coverage expansion from 14% tree coverage in 2010 to 20% tree-coverage in 2016, and providing a natural experiment

opportunity. For this pilot project, they propose to study the impact of this natural experiment by investigating whether the impact of tree-planting and the resulting greenness is evident with respect to AD. The 2010 to 2016 changes in greenness enable their team to deploy a population-based, prospective and longitudinal quasi-experimental design with established and scalable measures of AD and block-level greenness for a population-based sample of ~60,000 low-income Miami-Dade Medicare beneficiaries. The proposed study, therefore will examine the relationship of greenness to the incidence of new cases of AD, comparing diagnoses (ICD codes) in Medicare beneficiaries' records from 2010 and 2016. They will code the available universe of all ~9,000 low-income Census blocks in Miami-Dade County into three types of blocks: 1) Low-Low: low-green blocks in 2010 with no new tree plantings; 2) High-High: high-green blocks in both 2010 and 2016; and 3) Low-High Blocks: low green blocks in 2010 with post-2010 tree-plantings resulting in high greenness in 2016. Utilizing propensity scores as a statistical matching technique, they will randomly select 1,000 blocks in each of the three block types. The tests of the study aims will use multi-level modeling to assess the impact of greenness (High-High vs. Low-Low Blocks); and tree-plantings (Low-High vs. Low-Low Blocks) on incidence of AD. Current team collaborations extend across disciplines/sectors, including architecture, urban design, biostatistics, geography, public health, clinical practice and county government. In discussions during their poster session at the 2018 Alzheimer's Association International Conference (AAIC) and after a comprehensive literature review, it appears that their team is the first to examine neighborhood greenness and greening impacts on AD. If the pilot grant's initial results are promising, this study could merit consideration for an expanded study through other funding, such as an NIH R01, to investigate impacts of greenness and greening interventions on AD in areas beyond Miami-Dade County. This work has the potential to contribute to the field of AD prevention/ treatment through innovative community partnerships in policy and neighborhood-scale interventions that increase access to greenness and might serve to reduce the burden of AD in Florida and nationally. REFERENCES: (1) Brown SC, et al. (2018, March). IJERPH, 15, 430. (2) Brown SC, et al. (2018, July 25). Neighborhood greenness & AD in 249,405 Medicare beneficiaries. Poster presentation, AAIC, Chicago.

24. **Grant #9AZ24:** Middle-aged Offspring of Late Alzheimer's Proband: Novel Cognitive and Biomarker Assessment

**Principal Investigator:** David A. Loewenstein

**Organization:** University of Miami

**Abstract of Proposed Research:** The vast majority of cases diagnosed with Alzheimer's disease (AD) are considered late onset (LOAD). Previously, in a small cohort in Buenos Aires, Dr. Loewenstein's team of investigators found initial differences in middle-aged clinically asymptomatic offspring (O-LOAD) of one parent with late onset AD compared to age-equivalent controls. These included reductions in brain functional connectivity and volume, which were associated with a unique cognitive marker of preclinical AD, the failure to recover from proactive semantic interference (frPSI) on a novel cognitive stress test (Sanchez, Villarreal, Loewenstein, Guinjoan, et al., 2017; Abulafia et al., In Press). frPSI is a unique construct developed by Dr. Loewenstein and colleagues at the University of Miami and has increasingly been shown to be important in detecting preclinical AD (Loewenstein et al., 2017a) and has been strongly related to volumetric loss and cortical thinning in AD prone brain regions among those diagnosed

with amnesic mild cognitive impairment [aMCI] (Loewenstein et al., 2017a 2017b). Importantly, frPSI has been highly correlated with both total and regional brain amyloid load in asymptomatic community-dwelling elderly who otherwise obtained normal scores on a comprehensive traditional neuropsychological battery (Loewenstein et al., 2016). This has critical implications for early cognitive screening, selection for clinical trials and outcome measurement of AD- specific deficits as novel therapeutics become available. The proposed investigation provides an exciting and unprecedented opportunity to examine the underpinnings of the earliest manifestations of AD among a large group of well-defined middle-aged children who are offspring of one or more parents with late onset AD (O-LOAD). This would represent the first study conducted in the United States to evaluate frPSI in O-LOAD individuals. Age and educationally equivalent controls without any family history of LOAD will be used for comparison purposes. Unlike their small pilot study in Buenos Aires, this much larger O-LOAD cohort will undergo much more comprehensive neuropsychological assessment, and genetic analyses. Factors such as cognitive reserve, bilingualism and acculturation will be considered as important covariates. They will employ a combination of: a) a novel cognitive stress test, the Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L) uniquely sensitive to frPSI; b) fMRI measures of brain connectivity; c) structural MRI including diffusion tensor imaging (DTI); and d) genetic profile analyses. Sixty middle age O-LOAD participants will be compared to age and educationally equivalent controls without any family history of LOAD. The critically important data that will be provided by this proposed investigation will provide important insights related to the earliest changes in the brain among O-LOAD individuals through novel state-of-the-art cognitive stress tests tapping frPSI, structural and functional neuroimaging, and genetic profiles in this at-risk group. As such, they hope that this proposal will be competitive for State funding through the Ed and Ethel Moore program and provide the necessary preliminary data to prepare for submitting larger scale grant applications to the NIH. Finally, the obtained results should also have extremely important clinical and research implications for emerging treatment and prevention strategies.

25. **Grant #9AZ25:** Brain Vascular Imaging Phenotypes, Vascular Comorbidities and the Risk for Alzheimer Disease: The Florida VIP Study of AD Risk

**Principal Investigator:** Tatjana Rundek, PhD

**Organization:** University of Miami

**Abstract of Proposed Research:** The overarching goal of this proposal is to determine the impact of novel brain vascular imaging phenotypes (VIPs) and modifiable vascular comorbidities on cognitive and neurodegenerative profile typical of the Alzheimer's disease (AD) phenotype. Brain small vessel disease is the most prevalent cause of progressive cognitive impairment in the elderly. Magnetic resonance imaging (MRI) studies have shown the high prevalence of covert small-vessel disease in the elderly and population-autopsy series have verified the high frequency of the coexistence of vascular pathology with AD pathology. The need for quantitative evaluations of the impact of brain vascular phenotypes on cognitive and neurodegenerative changes related to AD pathology is evident. To achieve this goal Dr. Rundek and associates will leverage reach and in-depth brain magnetic resonance (MR) imaging, clinical and neurocognitive data from the NIH-funded 1Florida Alzheimer Disease Research Center (1FL ADRC), which enrolled a vulnerable population of South Florida with a large representation of Hispanics/Latinos. Available data in the 1Florida ADRC include MRI

and Amyloid positron emission tomography (PET) scans together with demographics and clinical and neuropsychological data. The MRI data has been quantified for brain volumetric and cortical thickness measures, which have already been used to identify the neurodegenerative changes (atrophy in selectively vulnerable brain regions) typical of AD. A major effort in this application will be to measure and quantify new phenotypes of brain vascular disease pathology from collected MRI scans, which has been challenging, especially for small vessel disease, and has not reached a level of quantification similar to methods available for quantifying neurodegenerative changes. In the proposed study, they will utilize volumetric sequences from over 300 MRI scans to create a Vascular Imaging Phenotypes (VIPs), which will include silent brain infarcts, enlarged perivascular spaces, and volumes of regional white matter hyperintensity (WMH volumes), and visually-rated large vessel infarcts and cerebral microbleeds on gradient echo images. They will utilize novel automated MRI methods to quantify markers of small vessel disease and enlarged perivascular spaces. They will develop a vascular comorbidity (VasCOM) score utilizing data elements known to be associated with cardiovascular and cerebrovascular disease, from the extensive 1Florida ADRC demographic and clinical database. They will then integrate the VIPs and VasCOM score into a comprehensive model that will assess their impact on cognitive performance that are sensitive to detect individuals at increased risk of AD and on the severity of neurodegeneration on MRI and the amyloid load on amyloid PET scans in cognitively normal and mildly impaired 1FL ADRC participants. Their proposed research is of particular importance for Hispanic/Latino population of South Florida, which is the largest and fastest growing ethnic minority in the US. Hispanics/Latinos have a disproportionately high burden of vascular risk factors and comorbidities and they are largely underrepresented in AD research. Moreover, vascular comorbidities are modifiable and preventable. The results from the proposed investigations will uniquely position the team to start closing the gap in their understanding of the mechanisms by which vascular phenotype contribute to AD pathology and to inform future strategies to reduce AD risk specifically tailored to high vascular-AD risk populations.

26. **Grant #9AZ26:** Palliative Care Education in Assisted Living for Care Providers of Residents with Dementia

**Principal Investigator:** Debra Dobbs, PhD

**Organization:** University of South Florida

**Abstract of Proposed Research:** Assisted living (AL), which is home to almost one million older adults, has become an increasingly common setting for the provision of end-of-life (EOL) and palliative care (PC). AL communities are nonmedical, community-based residences that are not licensed as nursing homes (NHs); 4+ unrelated adults; and provide room and board, 24-hour supervised care for activities of daily living and respond to unscheduled needs. In Florida, the number of older adults who live in ALs has outpaced the numbers in nursing homes with 67,000 living in ALs in Florida. Of these, close to half have a diagnosis of dementia. Close to 300,000 older adults with serious illness die in AL. Hospice and PC is an effective approach for improving the quality of care for the dying. The goal of hospice and PC is to relieve suffering and to support the best possible quality of life for patients and their families. Residents in AL with dementia and without appropriate hospice and PC are more likely to be discharged to a nursing home or hospital, which is likely to result more often than not in a poor quality outcome. A PC education program for professional nursing staff facilitated by

hospice nurse educators in NHs has been shown to improve EOL care practices such as increases in hospice care, assessment and treatment of pain, and documented discussions of resident advance directives. The PI of this proposed study has adapted the PC program in NHs for AL nurses (Palliative Care Education in Assisted Living-PCEAL) and pilot tested it in two treatments and one control AL in a sample of mostly residents with advanced dementia. The study results show PCEAL to be a feasible intervention among nursing staff in collaboration with local hospices that approved the PCEAL for 6 continuing education units (CEUs). Dr. Dobbs and associates propose to conduct a two-year cluster randomized trial (CRT) among 12 ALs and residents (N=600) with a baseline, 3, and 6 months postintervention follow-ups to: 1) Examine the extent to which the PCEAL increases the assessment of pain; increases documentation of advance care planning; and increases rates of hospice admission in a sample of residents (N=600) from 12 Florida AL communities providing care to 50% or more with dementia diagnosis, while controlling for resident case-mix and facility level factors; and 2) Determine if improvements in resident care outcomes from the PCEAL program are mediated through increased staff knowledge about PC. PC education for direct care providers is an area of great need in AL. If the intervention proves to be effective to improve care for residents with dementia in AL with serious illness, this research has the potential to promote the widespread use of the PCEAL program, to educate nurses in AL to continue to improve the quality of EOL care for residents with dementia in AL settings.

27. **Grant #9AZ27:** A Pilot Study to Examine the Impact of an African Drumming for Dementia Program on African Americans with Mild Cognitive Impairment and Early Alzheimer's Disease and their Caregivers

**Principal Investigator:** Kyaien O Conner, PhD, LSW, MPH

**Organization:** University of South Florida

**Abstract of Proposed Research:** Alzheimer's disease (AD) has detrimental effects on the functional quality of life among community dwelling individuals living with AD and their caregivers. African Americans have a disproportionately high rate of AD and Mild Cognitive Impairment (MCI), experience a high-rate of AD-related health disparities, are underrepresented in AD research and are less likely to be evaluated and treated during early stages of the disease. This highlights the urgent need to develop and assess culturally relevant, nonpharmacological interventions, which may help to improve daily functioning and quality of life of community dwelling African Americans living with Alzheimer's disease and related disorders (ADRD) and their caregivers. Music interventions are low-cost, minimal side-effect interventions with numerous benefits. Multiple studies suggest music interventions result in improvements in anxiety and depression, agitation, autobiographical memory recall, and a variety of cognitive functions among individuals living with ADRD. Drumming as a music intervention is uniquely beneficial for individuals with dementia disorders, allowing them to participate in activities that can impact physical, psychological and cognitive health (e.g. rhythmic body movement, auditory stimulation, social interaction, and chanting etc.). African drumming may be particularly beneficial for African Americans living with mild cognitive impairment (MCI) and early-stage AD and their caregivers. This culturally relevant and personalized approach to a music intervention has the potential to impact a range of social, cognitive, psychological and behavioral outcomes; however, there is a dearth of research which has empirically examined African Drumming as a therapeutic mechanism for this population. Dr. Conner and team propose a pilot open trial whereby

they will examine the impact of African Drums for Dementia for community dwelling African Americans living with MCI and early-stage AD (N= 30) and their caregivers (N=30). The aims of this novel pilot project are to: 1.) manualize and implement the African Drums for Dementia program; 2.) assess the feasibility and acceptability of this program; 3.) assess and measure outcomes for persons living with MCI and early-stage AD (i.e. cognitive function, mood, quality of life, and self-esteem) and caregivers (i.e. overall satisfaction with the program, caregiver burden, mood, self-perceived community support, quality of life and self-esteem). Culturally relevant non-pharmacological approaches to optimize the functioning of African Americans living with Alzheimer's disease, reduce caregiver stress and provide person-centered care practices are urgently needed. Their project directly aligns with program goals to develop and assess interventions to reduce caregiver burden and enhance the social environment of individuals living with Alzheimer's disease and Related Disorders (ADRD). They expect results from this pilot to provide preliminary evidence that African Drumming is an inexpensive, and culturally meaningful therapeutic mechanism that can address measurable improvements for African Americans with ADRD and their caregivers that can be sustained in community settings.

28. **Grant #9AZ28:** Visually-Assisted Mindful Music Listening Intervention for Persons Living with Dementia and their Caregivers: A Pilot Study

**Principal Investigator:** Hongdao Meng, PhD, MPH

**Organization:** University of South Florida

**Abstract of Proposed Research:** Alzheimer's Disease Related Dementias (ADRD) are among the most expensive medical conditions, affecting more than 5 million people in the United States. Family caregivers play a crucial role in the successful aging-in-place of older adults with ADRD, yet they assume these responsibilities with minimal support due to the informal nature of the care. Consequently, caregivers of patients with ADRD often suffer increased stress, depression, and anxiety. Many published interventions require multiple visits to the research centers for training. Frequent travel outside of the care setting imposes a hardship on caregivers to meet the wide range of their responsibilities. Therefore, there is an urgent need to develop new, innovative, and low-cost home and community-based interventions to reduce behavioral expressions among persons living with dementia (PLWDs) and enhance caregiver wellbeing. The objective of this study is to pilot-test and improve an existing classical music video collection and create a new Visually-Assisted Mindful Music Listening (VAMML) intervention, an innovative 4-group-session plus daily self-administered mindful listening sessions at the homes of PLWDs. The commercially available music video utilizes artfully interwoven nature and space imagery to engage participants' eyes in the process of listening to carefully chosen classical music and has been praised by individuals of all ages since its development by an award-winning musician in 2012. Dr. Meng and associates will synthesize the scientific evidence base for potential mechanism of action, develop a standard training manual for future implementation in the home and community setting. The team will partner with Senior Connection Center, Inc., the area agency on aging, to recruit volunteer participants. The primary aims of the study are: to determine the feasibility and acceptability of delivering the VAMML intervention to 20 caregivers of PLWDs; and to determine whether the intervention results in improved objective physiological measures, subjective psychological measures, sleep, mindfulness, and caregiver burden. After the successful completion of the study, it is expected to

demonstrate the feasibility and acceptability of the intervention, obtain key feedback regarding preferences for program delivery setting from PLWDs and their caregivers, and obtain a training manual for intervention delivery in the community settings (homes, senior centers, libraries, and universities). They will then formally test the modified VAMML intervention in a Stage II randomized controlled study in a research project grant (R01) application to be submitted to the National Institute on Aging (NIA). This line of inquiry is expected to provide consumers, health care providers/organizations, community organizations, researchers, and policymakers with important new information on low-cost, non-pharmacological interventions to reduce problem behaviors among PLWDs and improve wellbeing of their caregivers.

29. **Grant #9AZ29:** Intracellular anti-Tau Proteins Engineered on a Hyperthermophilic Scaffold

**Principal Investigator:** Jack M Webster, PhD

**Organization:** University of South Florida

**Abstract of Proposed Research:** Alzheimer's disease and related tauopathies are predominant neurodegenerative disorders afflicting the aging population. There is no cure and current treatments are designed to reduce the symptoms rather than treating the underlying cause. It is imperative to gain an understanding of the molecular cause and mechanisms of disease progression in order to develop novel therapeutic strategies to treat these diseases. Aberrant aggregation of tau protein into toxic oligomers, fibrils and tangles has emerged as a mechanism of neurodegenerative disease progression. Immunotherapy strategies utilizing antibodies that target aggregated conformations of tau protein are translating into clinical trials for the treatment of Alzheimer's disease and other tauopathies. While the application of antibodies has greatly changed the face of medicine, antibodies are not suitable to target tau in the cytoplasm of neurons, the site of initiation of aberrant tau aggregation. New tools must be developed to enable (and assess the value of) specifically targeting cytoplasmic tau oligomers and fibrils in pursuit of inhibiting tau aggregation and disease progression at an earlier stage. To address this need, Dr. Webster and his team will develop conformation-selective tau-binding proteins that are fully functional in an intracellular, cytosolic, reducing environment. They will exploit a small non-antibody protein scaffold, the Cold Shock Protein from a hyperthermophilic organism (TmCSP), possessing characteristics which make it an ideal candidate for intracellular targeting; it is a hyper-stable, disulfide-free, independently folded, monomeric protein with distinguishable surface exposed amino acid sidechains which enable engineering of novel binding sites. The development and evaluation of these non-antibody tau-binding proteins will be accomplished according to the following aims. Aim1: Develop TmCSP libraries and screen for conformation-specific binders. They will develop and screen phage display libraries each containing ~1 billion variants of TmCSP in order to engineer novel monomer-specific, oligomer-specific and fibril-specific tau-binding proteins. They will use Surface Plasmon Resonance binding analysis (Biacore) to evaluate affinities of their lead constructs for binding to tau oligomers and fibrils. Aim 2: Evaluate and select lead constructs based on effects on tau in vitro and in cellular models. They will evaluate whether lead constructs modulate aggregation of recombinant tau protein in vitro. They will use cell models to evaluate the ability of TmCSP constructs to modulate tau phosphorylation, aggregation and secretion; three events influencing tau pathology and disease progression. Tau-targeted TmCSP proteins will enable the study of conformation-specific tau modulation specifically in the

cytoplasmic compartment. Conformation-specific anti-tau TmCSP agents derived from this work may also translate to therapeutic, diagnostic imaging and circulating biomarker detection applications.

30. **Grant #9AZ30:** Impact of Adapted Dance on Mood and Physical Function among Alzheimer's Disease Assisted Living Residents

**Principal Investigator:** Crystal Bennett, PhD, RN

**Organization:** University of South Florida

**Abstract of Proposed Research:** Alzheimer's disease (AD) and related dementia disorders is the most common neurodegenerative disease in older adults and is the 6th leading cause of death in the U.S. Almost 40% of Assisted Living residents have an AD or dementia diagnosis. Secondary symptoms of AD that are challenging to manage in the assisted living facility (ALF) and contribute to significant caregiver burden are agitation and declines in physical function. These symptoms lead to greater dependence on ALF staff and caregivers for assistance with activities of daily living. This is a pilot research project that will address Focus Area 1.1 Behavioral and will assess whether adapted dance improves psychological and physical secondary symptoms of AD in Northwest Floridians. Dance is a promising intervention that can improve mood, physical function and improve quality of life in older adults, including those with neurological conditions. However, adapted dance is not offered to those with AD in Northwest Florida ALF communities. Whether adapted dance can improve agitation in those with AD residing in the ALF is not clear. Addressing this knowledge gap could support the use of adapted dance to improve quality of life in the AD population specifically in Northwest Florida. This project innovates by using a creative non-pharmacologic intervention to target secondary symptoms of AD. The aims for this project are: 1) Assess the effects of adapted dance on agitation. 2) Assess the effects of adapted dance on balance, gait, and lower extremity function. 3) Explore if perceived caregiver stress changes while the AD resident participates in dance. Dr. Bennett and her team hypothesize that adapted dance improves agitation, balance, gait, and lower extremity function through mechanisms of dance. A quasi-experimental design will be used with AD residents to complete 12 weeks of adapted dance. At pretest, six weeks, and at 12 weeks, measures will be collected for agitation, balance, gait, lower extremity function, and caregiver stress. Participants will be randomly assigned to the dance or control group. The control group will participate in a socially engaging but nonphysical activity. At conclusion of the 12 weeks, the control group will then participate in the dance intervention for the same time period. Recruitment will take place in Northwest Florida ALFs. Residents will be screened for study participation using the Montreal Cognitive Assessment to assess cognitive ability and the Timed-up-and go test to assess mobility. Testing and the intervention will take place in Northwest Florida ALFs. The 12-week adapted dance intervention will be a low impact dance routine where one foot is always in contact with the floor. Adapted dance can be modified specifically for those with cognitive and mobility limitations. The classes will be led by the principal investigator, a licensed registered nurse of 23 years, who has experience with AD residents and the intervention. Measurements of outcomes will include using the Cohen-Mansfield Agitation Index and the Neuropsychiatric Inventory Clinician Rating Scale to assess agitation, the Short Physical Performance Battery to assess balance, gait, and lower extremity function, and the Zarit Caregiver Burden Scale to assess caregiver stress.

**APPENDIX B**  
**FISCAL YEAR 2018-2019 ACTIVE GRANTS**  
(Funding Year 2017-2018)

Grant #	Organization	Principal Investigator	Award Amount	Life To Date Expenditure	Unspent Funds	Executed Date	End Date	Patents	Publications	Follow-on Funding
8AZ01	Ave Maria University	Barbosa, Antonio	\$ 100,000	\$ 54,167	\$ 45,833	02/07/2018	02/28/2019	No	No	No
8AZ02	Florida Atlantic University	Modi, Jigar	\$ 100,000	\$ 32,000	\$ 68,000	03/19/2018	02/29/2020	No	No	No
8AZ03	Florida Institute of Technology	Liao, Yi	\$ 100,000	\$ 31,250	\$ 68,750	02/09/2018	02/28/2020	No	No	No
8AZ04	Florida International University	Nair, Madhavan	\$ 224,643	\$ 32,760	\$ 191,883	02/28/2018	02/28/2022	No	Yes	No
8AZ05	Florida State University	Carretta, Henry	\$ 100,000	\$ 29,166	\$ 70,834	02/01/2018	02/28/2020	No	No	No
8AZ06	Mayo Clinic Jacksonville	Murray, Melissa Erin	\$ 221,000	\$ 42,973	\$ 178,027	02/12/2018	02/28/2021	No	Yes	No
8AZ07	Mayo Clinic Jacksonville	Liu, Chia-Chen	\$ 221,000	\$ 42,973	\$ 178,027	02/14/2018	02/28/2021	No	No	No
8AZ08	Mayo Clinic Jacksonville	Lucas, John A.	\$ 200,000	\$ 38,704	\$ 161,296	02/08/2018	02/28/2021	No	No	No
8AZ10	Mayo Clinic Jacksonville	Ebbert, Mark T. W.	\$ 100,000	\$ 33,332	\$ 66,668	02/13/2018	02/28/2019	No	Yes	No
8AZ11	Mount Sinai Medical Center	Duara, Ranjan	\$ 96,643	\$ 8,053	\$ 88,590	05/21/2018	04/30/2020	No	No	No
8AZ12	University of Central Florida	Teter, Kenneth	\$ 200,000	\$ 25,002	\$ 174,998	04/09/2018	02/28/2022	No	No	No
8AZ13	University of Central Florida	Hernandez, Florencio	\$ 200,000	\$ 58,331	\$ 141,669	03/05/2018	02/28/2020	No	No	No
8AZ14	University of Central Florida	Sikorska-Simmons, Elzbieta	\$ 95,784	\$ 27,937	\$ 67,847	03/05/2018	02/28/2020	No	No	No
8AZ15	University of Florida	Kesavalu, Lakshmyya	\$ 221,000	\$ 64,456	\$ 156,544	02/21/2018	02/28/2020	No	No	No
8AZ16	University of Florida	Chakrabarty, Paramita	\$ 221,000	\$ 32,228	\$ 188,772	02/08/2018	02/28/2022	No	No	No
8AZ17	University of Florida	Cottler, Linda B.	\$ 200,000	\$ 38,892	\$ 161,108	03/05/2018	02/28/2021	No	No	No

8AZ18	University of Florida	Yachnis, Anthony T.	\$ 99,987	\$ 16,664	\$ 83,323	01/25/2018	02/28/2020	No	No	No
8AZ19	University of Florida	Streit, Wolfgang J.	\$ 96,643	\$ 28,189	\$ 68,454	02/01/2018	02/28/2020	No	No	No
8AZ20	University of Florida	Xu, Guilian	\$ 99,577	\$ 29,043	\$ 70,534	02/21/2018	02/28/2020	No	No	No
8AZ21	University of Miami	Curiel, Rosie	\$ 89,304	\$ 52,094	\$ 37,210	02/28/2018	02/28/2019	No	Yes	No
8AZ22	University of Miami	Alperin, Noam	\$ 221,000	\$ 64,456	\$ 156,544	02/16/2018	02/28/2020	No	Yes	No
8AZ23	University of Miami	Loewenstein, David	\$ 450,844	\$ 131,495	\$ 319,349	02/14/2018	02/28/2020	No	No	No
8AZ24	University of Miami	Toborek, Michal	\$ 221,000	\$ 32,228	\$ 188,772	02/07/2018	02/28/2022	No	No	No
8AZ25	University of Miami	Griswold, Anthony	\$ 100,000	\$ 58,331	\$ 41,669	02/27/2018	02/28/2019	No	No	No
8AZ26	University of Miami	Dykxhoorn, Derek	\$ 200,000	\$ 58,331	\$ 141,669	02/14/2018	02/28/2020	No	No	No
8AZ27	University of South Florida	Selenica, Maj-Linda B.	\$ 100,000	\$ 29,169	\$ 70,831	02/09/2018	02/28/2020	No	No	No
8AZ28	University of South Florida	Nash, Kevin	\$ 100,000	\$ 29,169	\$ 70,831	02/08/2018	02/28/2020	No	No	No
8AZ29	University of South Florida	Kang, David E.	\$ 221,000	\$ 64,459	\$ 156,541	02/06/2018	02/28/2020	No	Yes	No
8AZ30	University of South Florida	Lee, Daniel C.	\$ 200,000	\$ 29,167	\$ 170,833	02/23/2018	02/28/2022	No	No	No
8AZ32	The Roskamp Institute, Inc.	Keegan, Andrew	\$ 99,576	\$ 29,043	\$ 70,533	03/02/2018	02/28/2020	No	No	No

**ACTIVE RESEARCH GRANTS FISCAL YEAR 2018-19  
(Funding Year 2017-2018)**

1. **Grant #8AZ01:** Inhibiting Alzheimer's Disease by Modulating a Key Player in Plaque and Tangle Formation, SIRT1, by Regulating the Formation of Nicotinamide Metabolites

**Principal Investigator:** Antonio Barbosa, PhD

**Organization:** Ave Maria University

**Progress Report:** Significant progress has been made to understand the protein pathology of Alzheimer's disease (AD). Nonetheless, it is unclear why some individuals develop AD. Increasing evidence suggests that AD is linked to changes in the metabolic profiles of patients. Therefore, Dr. Barbosa and associates propose to elucidate the mechanisms by which metabolites affect the key metabolic protein sirtuin1 (SIRT1) to promote neuron survival. SIRT1 is a deacetylase that serves to prevent the formation of pathogenic Tau tangles by deacetylating Tau, leading to its proteasomal degradation. Furthermore, SIRT1 deacetylation leads to a retinoic acid receptor-mediated (RAR-mediated) inhibition of amyloid beta plaque build-up. Indeed, the modulation of SIRT1 activity has been previously shown to benefit AD pathology in murine models by reducing AD-associated Tau tangles and amyloid beta plaques.

When SIRT1 is active, its substrate nicotinamide adenine dinucleotide (NAD<sup>+</sup>) is converted to nicotinamide (NAM). N-nicotinamide methyltransferase (NNMT), in turn, methylates NAM to Me-NAM. Me-NAM was once considered an inactive metabolite but has been shown to stabilize SIRT1 in liver cells. They hypothesize that an increase in NNMT activity will result in an increase of the metabolite Me-NAM. They next hypothesize that increased Me-NAM levels will promote SIRT1 stabilization.

This pilot grant application proposes to address the major grant priority area of novel therapeutic targeting strategies (Focus Area 2.1) by investigating the biochemical mechanism of Me-NAM stabilization of SIRT1 (Aim 1), developing an assay to detect NNMT activity via production of Me-NAM (Aim 2), and performing a small-scale screen to identify NNMT modulating compounds (Aim 3). To do this, they have established a multi-investigator team of researchers in medicinal chemistry, biology, and biochemistry.

Low expression of "SIRT1.1" from a SIRT1 expression vector obtained from Addgene was obtained. Custom expression of a plasmid with codon-optimized full-length SIRT1 will be constructed.

SIRT1 enzymatic assays using purified SIRT1 and a commercial SIRT1 kit have been carried out. The enzyme performance was optimized in the assays by screening different reaction times. The synthesized SIRT1 drug candidates were tested in the assay and some apparent activation of SIRT1 has been observed.

An expression optimization study of NNMT was performed. It appears that hexa histidine tagged (His6x-tagged) NNMT can be expressed well in E coli with isopropyl  $\beta$ -D-1

thiogalactopyranoside (IPTG) induction times of up to 3 hours. A protein that appears to be aldehyde oxidase, an enzyme that may be used to detect NNMT activity is partially purified. The synthesis of a chemical reactant to be used to develop a new Me-NAM sensor has begun.

Synthesis of SIRT1 activators. Analysis of the SIRT1720- SIRT3 co-crystal structure yields several opportunities to design a novel chemical series by making meaningful structural changes to the sirtuin-activating molecule. Synthesis of three SIRT1 agonists have been completed. Synthetic troubles have required the redesign of the synthesis of two analogs and progress on additional analogs are in progress.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** This project is in collaboration with the Department of Chemistry and Physics as well as the Department of Biology at Ave Maria University. During the Summer of 2018, five undergraduate interns worked on the project. In the regular school semester, seven other students were involved on the project alongside four faculty members (Antonio Barbosa, PhD, Stephen Cronin, PhD, James Vranish, PhD, and Diana West, PhD).

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

2. **Grant #8AZ02:** Neuroprotection of GCSF Gene Therapy in Alzheimer's Disease

**Principal Investigator:** Jigar Modi, MD, PhD

**Organization:** Florida Atlantic University

**Progress Report:** The purpose of the project for the period from March 19, 2018 to September 30, 2018 is to determine which granulocyte-colony stimulating factor (GCSF) gene vectors that Dr. Modi and associates designed provides the best results in cell-based or animal-based Alzheimer's disease (AD) models based on the molecular and cellular biomarkers and functional tests. The molecular and cellular biomarkers used for cell-protection and cell survivals include B-cell lymphoma 2 (Bcl-2), and OPA1 (mitochondrial dynamin like GTPase) and those used for cell stress/injury and cell death include C/EBP homologous protein (CHOP), 78-kDa glucose-regulated protein (GRP78), Dynamin-related protein 1 (DRP1) and Beclin 1. The highlights of the progress made during this period are summarized as follows: (1) Delivery of AAV-hGCSF gene vectors to mice via eye drop method and demonstration of expression of hGCSF protein in the brain. The presence of hGCSF mRNA in the brain after infection with AAV-CMV-hGCSF; AAV-SYN-hGCSF and AAV-SYN-HRE-hGCSF gene therapy was confirmed using real time polymerase chain reaction (PCR), real-time quantitative reverse transcription (qRT-PCR). In addition, the expression of human granulocyte-colony stimulating factor (GCSF) protein (hGCSF) was confirmed by immunoblotting test using specific antibodies against hGCSF. (2) Demonstration of the efficacy of the delivered GCSF gene therapy in cell-based AD model, namely, protection of Amyloid-  $\beta$  ( $A\beta$ ) induced cell injury in PC-12 cells by AAV-CMV-GCSF, AAV-SYN-GCSF, AAV-HRE-SYN-GCSF gene vectors. (3) Demonstration of the efficacy of the delivered GCSF gene therapy in animal stroke model by showing a reduction of stress markers for endoplasmic reticulum (ER), e.g.,

GRP78, CHOP and Caspase-12, for autophagy marker, e.g., Beclin-1 and for mitochondrial marker, DRP1 and enhancer for mitochondrial functions e.g., OPA1 and in addition to behavioral functional test, namely, the locomotor activity test. The locomotor activity was found to be significantly improved by GCSF gene therapy with AAV-HRE-SYN-hGCSF which is in general consistent with the results obtained from molecular biomarkers analysis. This supports their hypothesis that presence of the hypoxia-response promoter (i.e., HRE) is critical for AD gene therapy. (4) Elucidation of the mechanism of AAV-hGCSF gene therapy in triple transgenic (3xTg) AD model including both neuro-protection and neuro-regeneration. The neuro-protective mechanism is supported by a reduction of cell stress markers and an increase of pro-cell survival markers after GCSF gene therapy as stated above in 3. The neuro regeneration mechanism is supported by the observations that an increase of ChAT (Choline Acetyl Transferase), a marker of Cholinergic neurons and decrease of  $\beta$ -Amyloid ( $A\beta$ ) protein, a marker of neurodegeneration was obtained using qRT-PCR and immunoblotting test after GCSF gene therapy. The increased level of ChAT and decrease level of  $A\beta$  in 3xTg-AD mice model after administration of GCSF gene therapy suggesting that G-CSF gene therapy further delays the process of neural degeneration in the AD model.

**Follow On Funding:** None at the time of reporting.

**Collaboration:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

3. **Grant #8AZ03:** CO Releasing Polymer Nanoparticles for Treatment of Alzheimer's Disease

**Principal Investigator:** Yi Liao, PhD

**Organization:** Florida Institute of Technology

**Progress Report:** This is a newly awarded grant started from 02/09 this year. The abstract and the progress are listed below: Abstract: This is a pilot project aiming at development of a nanomedicine for Alzheimer's disease (AD). More than 35 million people worldwide suffer from AD including about 5.5 million Americans. Currently, there is no cure for AD. Although carbon monoxide (CO) is known as a toxic gas, it is actually naturally produced in small quantities and plays important roles in biological functions. Studies in the past two decades have shown many beneficial effects of CO. It was found that level of CO increased in the brains of AD patients. A later study showed that Heme oxygenase-1 produced CO to protect brain cells from damage caused by amyloid related to AD, which is consistent with the neuroprotecting effects of CO suggested by many studies. Since CO is toxic at high level, control over the dose of CO is important. Carbon monoxide releasing molecules (CORMs) have been studied in the past decade for controlled release of CO. Beneficial effects of a CORM on brain cells have been demonstrated by a in vitro study. However, there is no report showing that the CORM can pass blood-brain barrier. In this project, Dr. Liao and associates will develop brain-delivery polymer nanoparticles loaded with CORMs and study their CO releasing profile. These nanoparticles are expected to be able to release CO in the brains of AD patients,

strengthen the self-protecting measures naturally adopted, and ease the symptoms of AD. The brain-delivery nanoparticle is based on polysorbate 80-coated polybutylcyanoacrylate (PBCA) nanoparticle, which has been widely used to deliver different drugs to brain. Two types of CORMs will be loaded to the nanoparticles. The first type of CORM releases CO through a hydrolysis mechanism. The second type releases CO upon photo- irradiation and thus can be selectively activated at the sites where amyloids are observed. Results of this pilot project will allow the therapeutic effects of CO on AD to be carefully studied and the related drugs to be developed in the future.

The PBCA has been prepared using both radical and anionic polymerization methods. Additionally, PBCA nanoparticle has been prepared using a unconventional nano-precipitation method, and coated with polysorbate 80. Dynamic light scattering study showed that the nanoparticle has an average size of 200 nm and a narrow polydispersity, which are suitable for drug delivery according to literature. They have developed a new photoCORM, which is more convenient to use than the same type of CORM developed before due to its hydrophobicity and solid form. They are currently studying its CO releasing property and will load it to the PBCA nanoparticle. They have synthesized the key intermediate  $\text{NMe}_3\text{H}_2\text{BCOOH}$  for preparation of the proposed boron CORMs, which release CO via hydrolysis. Lastly, they attempted to prepare a boron CORM using the intermediate and a triazole ligand designed for fast CO release. However, experimental results showed that the ligand was too weak to link to the boron. They are currently preparing the same type of CORM using vitamin B3 as the ligand.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** The project is conducted by collaboration between the PI, Yi Liao and co-PI Rudolf Wehmschulte. PhD students Hussam Alhamza, Adnan Elgattar and MS student Almutasim Alwagdani are working on the project.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

4. **Grant #8AZ04:** Therapeutic Role of Withaferin A and CRID3 in the Prevention of AD. A Novel Nanotechnology Approach

**Principal Investigator:** Madhavan Nair, PhD

**Organization:** Florida International University

**Progress Report:** Alzheimer's disease (AD) is a growing threat to healthcare in the aging population and is marked by the accumulation of amyloid beta deposition in the brain and the pathology is enhanced by neuroinflammatory process. Inflammasomes are recently known multiprotein signaling complexes and are known to trigger inflammatory proteins such as interleukin 1 beta (IL-1beta) that is known to play a significant role in the genesis of AD. Among the inflammasome complexes, a nucleotide-binding oligomerization domain-like receptor, NLR Family Pyrin Domain Containing 3 (NLRP3) and nuclear factor kB (NFkB) are the major neuroinflammatory pathways that lead to

AD. Therefore, therapeutic drugs which can target both NFkB and NLRP3 activation will play a major role in reducing amyloid beta levels and prevention of neuropathology of AD. In preliminary studies, Dr. Liao's team reported for the first time that Withaferin A (WA), an extract from *Withania somnifera* plant, known to inhibit NFkB activation, improved synaptic plasticity and neuronal spine density; and significantly inhibited amyloid beta production and amyloid beta induced neurodegeneration. Furthermore, the research team have also demonstrated that cytokine release inhibitory drug 3 (CRID3), an inhibitor of NLRP3 significantly prevented neuroinflammation in their in vitro model system. Therefore, use of these therapeutic drugs targeting both NFkB and NLRP3 will have a translational significance in the prevention of neuroinflammation and associated neurodegeneration in AD patients. However, these drugs are impenetrable to the brain to prevent neuroinflammation and subsequent neurodegeneration. The use of nanotechnology in medicine has exciting prospects for the development of a novel drug delivery system to the brain across the Blood Brain Barrier (BBB). Their recently described manuscript and patented technology (US20130317279 A1 and WO patent: CT/US2013/068698) that describes magnetoelectric nanoparticles (MENPs) as a novel drug carrier which offers unique capabilities including its low energy and dissipation-free on-demand drug release across BBB. Accordingly, research staff will use MENPs as a carrier molecule to deliver WA and CRID3 across BBB to inhibit the NFkB and research staff will use MENPs as a carrier molecules to deliver WA and CRID3 (sodium salt) across BBB to inhibit the NFkB and NLRP3 mediated neurodegeneration in AD using their patented novel nanotechnology approach: Thus in the Aim #1 : the effect of Withaferin A and CRID3 will be investigated for the inhibition of amyloid beta induced NFkB and NLRP3 activation, respectively and associated down-stream inhibition of pro-inflammatory cytokines and amyloid beta production in mixed in-vitro microglia and SH-amyloid precursor protein (APP) (APP over expressing SH-SY5Y neuronal cell line) cell culture models. In specific Aim #2, the research team will develop and characterize MENP bound WA and CRID3 within the liposomes (to increase the drug stability, bioavailability and target specific brain delivery of these drugs): and study its non-invasive BBB transmigration, on-demand controlled release and therapeutic efficacy of the developed cargo using the in-vitro BBB model: while specific Aim #3 will study the therapeutic efficacy (synaptic plasticity and neurobehavioral) of this novel nanoformulation in APP/PS1 (presenilin 1) AD mouse model.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Tiwari, S., Atluri, V.S.R., Arias, A.Y., Jayant, R.D., Nair, M., et al. (2018). Withaferin A suppresses Beta amyloid in APP expressing cells: Studies for Tat and Cocaine associated neurological dysfunctions. *Frontiers in Aging Neuroscience* 10

**Patents:** None at the time of reporting.

5. **Grant #8AZ05:** Disparities in Health Services Utilization Across Racial/Ethnic Groups Among Persons with Alzheimer's Disease and Related Conditions

**Principal Investigator:** Henry Carretta, PhD, MPH

**Organization:** Florida State University

**Progress Report:** The purpose of this study is to understand the association of individual characteristics of people on the observed differences in health outcome measures for racial minorities as compared with the Caucasian population among persons with Alzheimer's Disease and Related Conditions (ADRC). An additional purpose of the study is to understand the relationship between where a person lives (in this case Florida counties) and observed differences in ADRC health outcome measures between racial minorities and Caucasians. Dr. Carretta and associates are interested in understanding how factors outside of an individual can impact a person's health and opportunities for improved life opportunities are sometimes referred to as the Social Determinants of Health (SDOH).

Some individuals, families and communities appear to have more resilience to hardship than others. In this case, resilience is understood as the ability to face the collective challenges of an individual's life circumstances including their health and factors they are exposed to by virtue of where they live, e.g. crime vs. a close-knit supportive community. Some Florida counties have higher or lower levels of factors associated with positive and negative influences on the SDOH. Some minority communities appear more able to overcome the disadvantages and life experiences and have health outcomes that are as good as or better than some advantaged populations. The unexpectedly good outcomes in these populations are believed to be related to the level of resilience among some individuals and communities. This study aims to identify Florida counties that are achieving better ADRC health outcomes than expected based on the characteristics of the individuals and the Florida County in which they reside.

The study utilizes a large collection of medical claims and surveys of the Medicare population to construct measures of health outcomes, individual and neighborhood characteristics to study the ADRC population in Florida. The data requires intensive preparation in order to conduct the analysis. Six months into the grant period they have made significant progress in preparing their individual-level data for analysis. Significant work remains to integrate county level measures of the SDOH with the data of individuals' health outcomes in prior to beginning the analysis.

The study is at an early stage and had produced no health outcome results or measurable return on investment. Identification of Florida counties with better than expected ADRC health outcomes will lead to more extensive study of the specific factors are most important in predicting unexpected positive health outcomes. Recommendations on how to address changeable factors can then be developed.

**Follow On Funding:** None at the time of reporting.

**Collaboration:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

6. **Grant #8AZ06:** Quantitative Neuropathology and Biochemistry of Survival Differences in Hispanic Americans with Alzheimer's Disease

**Principal Investigator:** Melissa Erin Murray, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** In the next few decades, the United States population will become proportionally older and more ethnoracially diverse, contributing to a projected increase in the prevalence of dementia. By 2030, approximately one in five Americans will be over the age of 65 and, by 2060, Hispanic Americans and black/African Americans are projected to constitute 29% and 14% of the population, respectively. The prevalence of dementia is estimated to more than double by 2050. Despite these trends, the understanding of dementia across ethno-racial groups remains limited and represents an important topic of investigation. The extent to which neuropathologic (*i.e.*, brain disease changes) and genetic factors contribute to disparities in cognitive deficits among ethno-racial groups remains poorly understood. Thus, clinical, genetic, and neuropathologic differences were investigated in Alzheimer's disease (AD) across three ethno-racial groups from the Florida Autopsied Multi-Ethnic (FLAME) study. The primary goal was to assess demographics, apolipoprotein E (*ApoE*) genotype, clinical progression and neuropathologic differences or similarities in the context of autopsy-confirmed AD. Individuals who are seen by participating Memory Disorder Clinics throughout the State of Florida can register for autopsy regardless of sex, race, or ethnicity. The major requirement is that a documented neurologic or psychiatric work-up for cognitive disorders be available. Participating centers include West Florida Regional Medical Center, Tallahassee Memorial, Mayo Clinic Jacksonville, University of Florida, Orlando Health Center for Aging, Florida Hospital Orlando, East Central Florida, Morton Plant, University of South Florida, St. Mary's Medical Center, Florida Atlantic University, Sarasota Memorial, Lee Memorial, Broward Health North, University of Miami, and Mount Sinai Medical Center. All individuals in evaluated in this grant have come to autopsy and are thus referred to as decedent.

Demographic and clinical data were abstracted from available clinical history notes for the AD cohort, including self-reported sex and ethno-racial status that was available for all individuals. Years of education was available for n=952/1625 (59%) of all decedents. Job-level score was categorized based on an individual's highest occupation according to the United States Department of Labor occupation and was available for n=897/1625 (55%) of all decedents. Family history was based on self-reported presence of absence of apparent or diagnosed cognitive problems in any of the patient's family members and was available for n=1500/1625 (92%) of all decedents. Disease duration represented the time interval between age at symptom onset and death. Test date and score were recorded for every Mini-Mental State Examination (MMSE) [28]. At least one MMSE was performed in n=724/1625 (45%) of all decedents, and a final MMSE performed within three years of death was available for n=309/1625 (19%). Rate of cognitive decline was evaluated using three or more MMSE test dates relative to the date of death and calculated as points lost per year [22]; this was available for n=297/1625 (18%).

Individuals who reported that English was not their first language were given the option at each MMSE test date to take the English or Spanish version of the test. Family country of origin was reviewed for Hispanic decedents (available in 52/67 [88%]) and black decedents (available in all 19) who were neuropathologically-diagnosed with AD. Country of origin was sub-classified for Hispanic decedents as Caribbean (46/67 [68%]) or Latin American (6/67 [10%]) where applicable. This information was missing for 15 Hispanic decedents. All black decedents identified as having been born in the USA with the exception of one individual born in Guyana and another born in Jamaica. Primary language was not available for either of these cases; however, all other black decedents identified English as their primary language. Genetic screening of *ApoE*, the strongest genetic risk factor for AD, was available for n=1208/1625 (74%) of the AD cohort.

Through the support of the State of Florida funding, the abstraction of information has been completed. Moving forward, the purpose of the study will be to integrate specific measures of brain changes with the demographic and clinical information to hopefully identify similarities or differences that may impact individualized patient care.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Liesinger, A.M., Graff-Radford, N.R., Duara, R., Aziz A., Hinkle, K.M., Murray, M.E., et al. (2018). *Alzheimer's disease may not be more common in women, men may more commonly present younger with an atypical clinical syndrome: a retrospective study.* (Epub ahead of print) PMID: 30219939

Santos, O.A., Duara, R., Lucas, J.A., Greig-Custo, M.T., Murray, M.E., et al. (2018). *Clinicopathologic Study of Alzheimer's Disease from the Florida Autopsied Multi-Ethnic (FLAME) Cohort.* (Accepted with minor revisions)

**Patents:** None at the time of reporting.

7. **Grant #8AZ07:** Impact of TREM2 Variants on Microglial Function and Alzheimer's Disease Pathology

**Principal Investigator:** Chia-Chen Liu, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder with histopathological hallmarks of toxic amyloid- $\beta$  ( $A\beta$ ) plaques and neurofibrillary tangles in the brain. However, targeting  $A\beta$  alone has not yielded a disease-modifying cure, suggesting a multifactorial and complex nature of disease etiology. Interestingly, genetic studies have uncovered multiple genes enriched in microglia, a cell type responsible for immune surveillance in the brain, suggesting that microglia and related neuroinflammation are central to AD pathogenesis. Emerging evidence showed that microglial activation is a beneficial response in the early phases of AD, leading to increased  $A\beta$  clearance. However, at late stage, microglia may

paradoxically exacerbate the disease by secreting toxic pro-inflammatory cytokines in response to A $\beta$  and other pathologies. Thus, understanding how microglia and neuroinflammation contribute to the disease development and progression may help determine the therapeutic window and strategy for introducing mechanism-based therapy for AD.

Recent genetic studies showed that a rare Arg-47-His (R47H) mutation of the triggering receptor expressed on myeloid cells 2 (TREM2) significantly increases AD risk by 3-4 fold. TREM2 is an innate immune receptor primarily expressed by microglia in the brain and is involved in inflammation and phagocytic clearance of A $\beta$  and cellular debris. Although conflict data exist, TREM2 deficiency has been shown to increase A $\beta$  accumulation and neuronal loss in AD mouse models, suggesting that TREM2 in microglia is essential for limiting A $\beta$  deposition and related neuronal damage. However, it remains unclear how AD-associated TREM2-R47H mutation affects the functions of microglia and amyloid plaque development. To address this question, Dr. Liu and associates have recently developed novel mouse models that allow TREM2 wild-type (WT) or TREM2-R47H to be present only in microglia. The goal of their research is to determine how the AD-associated mutation, TREM2-R47H, affects inflammatory responses, neuronal function and memory performance. In addition, Dr. Liu and associates will examine how TREM2-R47H influences A $\beta$  metabolism, amyloid pathology, and A $\beta$ -associated microglia activation in the brain. They predict that this AD-associated mutation, TREM2-R47H, will impair microglia, enhance neuroinflammation and accelerate the development of AD.

They have successfully generated the animal models expressing human TREM2 WT or R47H mutant and are in the process of expanding the mouse colony. Upon induction, they demonstrated that TREM2 is specifically expressed in microglia, the major resident immune cells in the brain. They will perform the behavioral analysis to examine whether TREM2 and its associated inflammation affect memory performance. To investigate how TREM2 in microglia affects amyloid deposition, they are also generating amyloid model mice expressing TREM2. The success of their study should provide mechanistic guidelines as to how microglia-mediated neuroinflammation affects AD development and how they can target neuroinflammation and TREM2 in AD therapy.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

8. **Grant #8AZ08:** Evaluating the Impact of a Dementia-Caring Community Model on African Americans with Alzheimer's Disease and their Care Partners.

**Principal Investigator:** John A. Lucas, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** Ethnic minority communities often experience a disproportionate degree of health disparities related to Alzheimer's disease (AD) and dementia. African Americans in particular have a significantly higher prevalence of AD than Caucasians but typically do not seek evaluation until much later in the disease course. A number of sociocultural factors contribute to this disparity, including lack of dementia education, mistrust of the medical establishment, and limited knowledge of available resources. Communities can play an important role in helping residents with AD and their care partners obtain appropriate services and overcome the challenges and stigma of dementia that threaten quality of life, social well-being, and functional independence. The National Alzheimer's Project Act (NAPA) provides a roadmap to help communities become more 'dementia-caring', and the aim of the current study is to assess the impact of these methods on dementia knowledge, beliefs, and quality of life of African Americans with AD and their care partners.

**Methods:** A total of 166 community-dwelling African Americans have participated in this study to date. Of these, 111 participants reside in Jacksonville's New Town Success Zone, an underserved community that serves as the intervention site of this study. The New Town participants engaged in a dementia education presentation, followed by focus group discussions derived from the NAPA Dementia Friendly America toolkit. An additional 55 African American participants were recruited from a senior citizens center in the Jacksonville urban core, approximately three miles away from New Town. Urban core participants received identical dementia education, but this education was paired with an informal opportunity to socialize with dementia experts. Participants in both communities completed surveys of dementia knowledge and beliefs before and immediately after the education program. Approximately two months later, participants returned for a second visit, at which time dementia knowledge was re-assessed.

**Results:** Preliminary findings from this first phase of study suggest that factual knowledge of dementia assessed immediately after the educational experience improved significantly and equally in both conditions as compared to pre-test performance. Repeating the post-test approximately two months later revealed a mild loss of initially gained information; however, mean scores for both groups remained significantly better than pre-test scores.

Dementia-related beliefs were not assessed at the two-month study visit.

**Discussion:** Dr. Lucas' early findings reveal essential equivalence in dementia knowledge across the intervention (dementia-caring) and control (traditional lecture) groups. The longer-term impact of the intervention on dementia knowledge and beliefs will be further explored over the remaining course of the study. They expect findings will further inform their understanding of the potential scope and magnitude of outcomes that may be expected through dementia-caring initiatives in ethnic minority communities. Findings may also assist such communities in decision-making regarding resource allocation for such initiatives.

**Follow on Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

9. **Grant #8AZ10:** Identifying Drug Targets using Long-Read Sequencing In Alzheimer's Diseased and Control Brain Tissue

**Principal Investigator:** Mark T. W. Ebbert, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** Dr. Ebbert's manuscript detailing the ability of both PacBio and Oxford Nanopore sequencing platforms to traverse challenging repeat expansions was published in Molecular Neurodegeneration August 2018. The paper is entitled "Long-read sequencing across the C9orf72 'GGGGCC' repeat expansion: implications for clinical use and genetic discovery efforts in human disease." Molecular Neurodegeneration is a well-respected research journal with a 2017 impact factor of 6.426. This paper is a major boon for the research and has received significant attention, with more than 1500 article accesses, as of October 2018. This paper lays the foundation for future funding, demonstrating not only that these technologies are capable of accomplishing their aims, but also their ability to generate and analyze this cutting-edge data; having a citable publication demonstrating their ability to accomplish their aims is essential to attaining additional funding.

The paper, among other things, detailed an exciting new targeted approach from PacBio to determine how effectively this targeted long-read sequencing approach can traverse challenging DNA repeat expansions. Repeat expansions are becoming ever more recognized as important contributors in human disease. They are known to cause ALS, FTD, Fuch's disease, Fragile X Syndrome, and many more. A repeat expansion has even been implicated in Alzheimer's disease. As such, they needed to verify that the PacBio system is capable of sequencing through these repeats, which Dr. Ebbert's team have demonstrated in an important paper just accepted in Molecular Neurodegeneration.

Their paper targeted several known disease-causing repeat expansions, including the C9orf72 'GGGGCC' repeat expansion. The C9orf72 'GGGGCC' repeat expansion is may be the most challenging repeat to sequence because of its size (can be hundreds of thousands of nucleotides) and its pure guanine and cytosine (GC) content. DNA with high GC content are historically difficult to sequence. Their paper demonstrates that the long-read sequencing technologies they are employing are capable of traversing even the most difficult repeat expansion, and thus should be capable of sequencing any repeat expansions that may exist in Alzheimer's disease.

In addition to the work included in their publication in Molecular Neurodegeneration, they are preparing a second, higher-impact publication that includes new data on the ability of long-read sequencing technologies to address what are commonly referred to as 'dark'

genomic regions. These 'dark' regions are stretches of DNA that standard short-read sequencing approaches cannot accurately assess. Their work demonstrates the magnitude of the problem, identifying over 6000 genes that are at least partially 'dark' using short-read sequencing technologies. Early estimates suggest long-read sequencing from PacBio closes more than 50% of these regions. While long-read sequencing technologies are a great solution moving forward, there are already many large sequencing studies, including Alzheimer's disease, that have sequenced thousands of individuals using short-read technologies. They developed a computational method that can resolve many of these 'dark' regions in short-read data. They were able to rescue some valuable mutations that have been overlooked in Alzheimer's disease research. They are moving quickly to complete this research.

They have also generated long-read sequencing data on 20 Alzheimer's disease cases and controls and are preparing to take additional steps. The early results show great promise to discover mutations and RNA isoforms that have been overlooked in Alzheimer's disease. These data have been included in two larger grant submissions and they are preparing two NIH grants for submission next year.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Ebbert, M.T.W, Farrugia, S.L., Sens, J.P., Jansen-West, K., et al. Long-read sequencing across the C9orf72 'GGGGCC' repeat expansion: implications for clinical use and genetic discovery

**Patents:** None at the time of reporting.

10. **Grant #8AZ11:** Impact of the Modified MindSet Training Program on Maintaining Optimal Function Among Early Alzheimer's Patients and their Care Partners

**Principal Investigator:** Sindy Goenaga, MD, MPH

**Organization:** Mount Sinai Medical Center

**Progress Report:** This a novel adaptation of a program originally developed for cognitive training of persons with late mild cognitive impairment (MCI) and early Alzheimer's disease (AD). This pilot project capitalizes on the strengths of this previous work and adds a component designed to help the care provider become a therapy extender, increase communication skills of the care recipient (CR) and care provider (CP) as well as to provide stress management and increased coping skills. Cognitive evaluations with a battery of neuropsychological and functional tests and measures of stress and anxiety are administered before and after the six-week program to determine the impact of the program in every care recipient and care provider. A satisfaction survey is also conducted after the program is completed.

This is a unique and novel approach for dually treating both the CR and CP simultaneously which they believe will have a synergistic effect in producing

improvement for both members of the dyad. The CP will be a therapy extender by helping the CR with cognitive training homework and the intervention will be administered to dyads in a small group setting.

If successful, this dual target intervention will have substantial health impact in that it can enhance cognition and function in early AD patients and may reduce rate of cognitive decline and reduce both CR and CP's burden. Since depression and burden can lead to adverse outcomes such as physical illness and institutionalization this cost-effective non-pharmacological approach has a highly significant health implication.

This is a pilot study to examine the feasibility and acceptability of a novel intervention which provides simultaneous treatment to both the CR and the CP. An intention to treat (ITT) paradigm will be employed in a subsequent phase of this protocol, and additional funding for this protocol is currently being sought. The ITT paradigm includes every subject who is randomized according to randomized treatment assignment, ignoring non-compliance, protocol deviations, withdrawal, and anything that happens after randomization.

The results of this important pilot study can provide critical information to design and refine a larger scale trial that provides a brief intervention designed to improve the life of both care recipients and care providers. Thus far, one training group of 6 CR and CP dyads has been completed and another group is in progress. The following primary outcomes will be analyzed at the completion of the study: (1) change in cognitive measures and (2) change in quality of life measure. Anecdotally, there has been high satisfaction with the program, especially the aspect of increasing communication skills between CR and CP.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** University of Miami, Department of Psychiatry and Behavioral Sciences, Miami, FL (David A Loewenstein, PhD and Mathew Caplan, MHC)

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

11. **Grant #8AZ12:** Protein Disulfide Isomerase Uses Conditional Disorder as a Disaggregase Mechanism to Detoxify Amyloid Beta Fibrils

**Principal Investigator:** Kenneth Teter, PhD

**Organization:** University of Central Florida

**Progress Report:** Dr. Teter and his team propose that protein disulfide isomerase (PDI) can act as a "disaggregase" to dissolve and detoxify aggregated fibrils of the amyloid-beta (A $\beta$ ) peptide. Thus, recombinant PDI could be used as a novel therapeutic agent for the clearance of extracellular A $\beta$  fibrils. They will pursue this possibility by identifying the

minimal PDI fragment with disaggregase activity and the molecular mechanism for its neuroprotective function.

Since the grant start date of 4/9/18, they documented the ability of PDI to completely prevent A $\beta$  aggregation at a 1:10 molar ratio of PDI:A $\beta$ . The team also demonstrated that PDI can reverse the aggregation of A $\beta$  when added 4 h after the initiation of fibrillization but not when added 10 h after the initiation of fibrillization. Replicate experiments have confirmed these observations. This work provides proof-of-concept for the therapeutic application of PDI to dissolve nascent neurotoxic aggregates of A $\beta$ .

PDI has an abb'xa' structural organization that consists of two thioredoxin-like catalytic domains (a & a') separated by two non-catalytic domains (b & b') and an x linker. They predict the disaggregase activity of PDI is activated when substrate binding to the b domain transmits a signal through the b'x domains for unfolding of the a' domain. The expanded hydrodynamic size of the unfolded a' domain subsequently functions as a wedge to push against two or more peptides in the A $\beta$  aggregate. This provides a mechanical force to break apart nascent aggregates of A $\beta$ . In the context of this model, they purified a panel of PDI deletion constructs to evaluate the structural stability of PDI and its ability to undergo rounds of unfolding and refolding. Biophysical studies indicate that, consistent with their disaggregase model, the a' domain of PDI is more prone to unfolding than the rest of the protein but can still refold after denaturation. These observations provide new insight on the dynamic structural organization of PDI. Moving forward, the deletion constructs will be used to determine which domains of PDI are required for its A $\beta$  disaggregase activity.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

12. **Grant #8AZ13:** Optical Characterization of the Aggregation (Change in Size, Fibril Formation), Accompanying Structural Changes, and Membrane Pore Formation.

**Principal Investigator:** Florencio Hernandez, PhD

**Organization:** University of Central Florida

**Progress Report:** The purpose of this project is to provide a clearer picture of the mechanism of development of Alzheimer's disease by correlating specific structural factors of Amyloid Beta with their toxicity.

It is known that Alzheimer's disease is the most common form of dementia in people 65 years of age and older, and accounts for 60-70% of dementia. According to the 2013 Alzheimer's disease Facts and Figures, an estimated 5 million people suffer from Alzheimer's disease in the United States and the number of cases is projected to triple

by 2050. In the state of Florida there are more than 500,000 individuals with Alzheimer's disease, yet only 12% has been diagnosed. Alzheimer's disease is characterized by a progressive, irreversible deterioration of the patient's cognitive function. Many Alzheimer's patients, in the late stages of the disease, need 24/7 specialized care. Additionally, this disease is the sixth leading cause of death in the country and poses a large financial and social burden in families and society. Therefore, it has become a major public health concern and a research priority. Despite the tremendous basic and clinical research efforts, no effective therapies have been developed to treat Alzheimer's disease, mainly because the mechanism of development of the disease is still unresolved. By combining different expertise in optics, spectroscopy and biophysics, this research project promises to lead to a better understanding of the still mysterious mechanism. To achieve this goal, the research project staff are trying to elucidate what are the structural determinants of Amyloid Beta toxicity and how these structural features correlate with membrane binding and permeabilization in Alzheimer's disease.

This period the research staff determined the stability of different monomers and dimers of Amyloid Beta fragments in solution and found a correlation between their solubility and the likelihood to form aggregates. The most stable structural configuration is the hairpin-like arrangement, which becomes more stable as the length of the peptide increases. In the structure of the most cytotoxic Amyloid Beta 1-42 the peptide takes a hairpin-like configuration and aggregates by head-to-head tips. Calculations performed on this structure revealed, in agreement with recent experimental results on structure for this Amyloid Beta fibrils reported in Nature, that this type of fibril formation is produced by a specific electronic density distribution at the tips of the hairpin-like assembly.

During the last nine months the research staff was also capable to clarify the effect of lipids on the structural conformation of Amyloid Beta. It was showed that an increased amount of cholesterol induces the predominant formation of hairpin-like configuration in solution and becomes slightly distorted upon membrane binding and pore formation.

These novel results shed light on the potential mechanism of development of the disease and may open an avenue to understand the possible implications of the effect of cholesterol on the development of Alzheimer's disease.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** Six graduate students (Eduardo Romero, Christopher Felton, Leslie Davis, Nabin Kandel, Molla Manjurul Islam, Faisal Abedin) and two undergraduate students (Abdel Rahman Naser, Alea Sterling and Melanie Rodriguez) have been trained/mentored during the reporting period.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

13. **Grant #8AZ14:** Factors Influencing Family Caregivers' Medical Decision-Making for Patients with Advanced Alzheimer's Disease

**Principal Investigator:** Elzbieta Sikorska-Simmons, PhD

**Organization:** University of Central Florida

**Progress Report:** During this reporting period Dr. Sikorska-Simmons and associates 1) developed the study data collection procedures, 2) obtained the IRB approval for the study, 3) conducted the recruitment of 20 family caregivers for patients with advanced Alzheimer's disease, and 4) completed the first wave of 20 interviews. Each interview was done in person, lasted on average 1-2 hours and provided rich qualitative data about caregivers' experiences with medical decision-making in the context of advanced dementia. The most common decisions were those related to seeking diagnostic services and routine medical care. Dr. Sikorska-Simmons and associates are currently in the process of analyzing the qualitative data collected during the first wave of interviews. They also submitted a paper for presentation at the 14<sup>th</sup> International Conference on Alzheimer's & Parkinson's Diseases, Lisbon, Portugal, March 26-31, 2019 titled "Dementia and Medical Decision-Making from the Family Caregivers' Perspective." In addition, they are preparing a manuscript describing the study's conceptual framework and background literature for publication in the Journal of Gerontological Nursing.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

14. **Grant #8AZ15:** Periodontal Bacteria Augment Progression of Abeta; and Tau Pathology

**Principal Investigator:** Lakshmya Kesavalu, BVSc., MS, SCC

**Organization:** University of Florida

**Progress Report:** Purpose: Alzheimer's disease (AD) is a progressive loss of memory in which individuals experience memory decline that begin gradually and gradually worsen. Alzheimer's disease is a complex disease and the causes are not yet known with both environmental and genetic risk factors, contributing to its onset. Several epidemiological, clinical and molecular studies have shown that chronic gum disease in the mouth associated gum swelling and redness (co-morbidity or cofactor) is linked with increased risk and progression of varying forms of memory loss, including Alzheimer's disease. The purpose is to determine the possible causal association between gum disease bacteria with AD. There are two bacteria [Treponema denticola (T. denticola) periodontal bacteria and Streptococcus gordonii (S. gordonii) non-periodontal bacteria] are proposed to test their role in augmenting progression of Abeta and Tau Pathology in TgCRND8 (mouse model) and nonTgCRND8 mice model of AD-like amyloidosis.

Context: Numerous studies link gum disease associated chronic inflammation with increased risk of dementia, including AD. Plasma levels of antibodies to gum disease

bacteria are significantly higher in Alzheimer's disease patients. One study directly showed the presence of 7 different gum disease bacteria in Alzheimer's disease patient's brains. Dr. Kesavalu also observed oral bacteria component present in 4 out of 10 Alzheimer's disease brains.

They do not know the mechanism by which gum disease may be considered a risk factor for Alzheimer's disease.

**Progress:** The specific aims are to explore the gum disease bacteria *Treponema denticola* infection in regulating brain nerve damage in TgCRND8 mouse model of AD-like amyloidosis. Specific Aim 1. Investigate the role of *Treponema denticola* in regulating of amyloid  $\beta$  peptide (A $\beta$ ) plaque pathology in TgCRND8 mouse model of AD-like amyloidosis. Principal Investigator (PI) initiated transgenic (TgCRND8) and non-transgenic (nTgCRND8) mice breeding for specific Aim 1 study. Research project staff have selected male transgenic mice (12) from their existing breeding colony and ordered twelve 8-week-old wild-type female CB6 mice for breeding. Research project staff have 27 transgenic and 21 non-transgenic mice during breeding (first weaning) and genotyping.

Research project staff have 68 litters delivered (second weaning) and will be genotyped. Research staff are currently growing *Streptococcus gordonii* oral non-periodontal bacteria (Control) in anaerobic chamber. Research staff are growing fastidious anaerobic spirochete *Treponema denticola* strain CF734 (fluorescent protein labeled bacteria) and characterized culture, optical density, and enumeration. Planned to use for oral infection of TgCRND8 and nTgCRND8 mice in October 15, 2018. Research staff will use all mice for AIM 1 study.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

15. **Grant #8AZ16:** Towards Understanding the Biological Role of Newly Discovered Alzheimer's Disease Susceptibility Genes Affecting Immune Function

**Principal Investigator:** Paramita Chakrabarty, PhD

**Organization:** University of Florida

**Progress Report:** In this proposal, Dr. Chakrabarty and associates will conduct studies to understand the biological mechanisms underlying ABI family member 3 (Abi3) and phospholipase C Gamma 2 (Plcg2) mediated events that alter microglia function and Alzheimer's pathogenesis. For the first Aim, they had proposed generating mouse models of Alzheimer type amyloidosis that is deficient in either Abi3 or Plcg2 to assess how these genes affect Alzheimer-related neuropathologies (Aim 1).

This is the first legislative reporting period for their grant since the grant was funded in April 2018. During this period, they have:

a) initiated cross-breeding and have been maintaining and aging mouse colonies as described under Aim 1. Specifically, they have initiated breeding Abi3<sup>+/-</sup> mice from Jax Labs (B6N(Cg)-Abi3<sup>tm1.1(KOMP)</sup>Vl<sup>cg</sup>/J; Stock #028180) and Plcg2<sup>+/-</sup> mice from Dr. James Ihle at St. Jude's Children's Hospital to amyloid precursor protein (APP) transgenic (line TgCRND8) mice. Currently, their colony is aging so that they have enough mice for neuropathological characterization at 3 months and 6 months. The following genotypes are being generated:

APP<sup>+/-</sup>/Abi3<sup>+/-</sup>, APP<sup>+/-</sup>/Abi3<sup>-/-</sup> and APP<sup>+/-</sup>/Abi3<sup>+/+</sup> mice

APP<sup>+/-</sup>/Plcg2<sup>+/-</sup>, and APP<sup>+/-</sup>/Plcg2<sup>+/+</sup> mice

They have found that partially knocking out Abi3 reduces amyloid plaques. These mice were analyzed at 3 months of age. This is very exciting as this demonstrates that Abi3 gene has a direct role in modulating amyloid plaques in Alzheimer's disease. They are continuing to age the other genotypes to complete their study.

They are in the process of aging the APP/Plcg2 colony and they expect to have amyloid burden data in the next 6 months.

The researchers presented a poster describing their data at the 1st Southeastern Neurodegenerative Disease Conference jointly organized by University of Florida and Emory University at Orlando on September 27-29th. The poster was titled: Role of ABI3 in Alzheimer's type amyloid pathogenesis and the authors were Timothy Machula, Maria Yaroshenko, Pedro E Cruz, Danny Ryu, and Paramita Chakrabarty.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

16. **Grant #8AZ17:** Precision Public Health Approaches to Reduce Disparities in Memory Disorder Screening in Rural Minority Communities

**Principal Investigator:** Linda B. Cottler, PhD, MPH, FACE

**Organization:** University of Florida

**Progress Report:** Only one in 10 older adults who have Alzheimer's disease (AD) receives a diagnosis. Additionally, one in three older adults who die have AD. Early identification of cases can reduce healthcare costs. Therefore, it is critical to increase screening and identify AD cases, especially among rural residents and minorities. The aim of this project is to reduce health disparities for AD in mortality among older adults, 60 or older, in Florida by decreasing barriers to care. Target counties (Alachua, Putnam,

Marion, Bay, Calhoun, Gulf, Jackson, Washington, and Wakulla) in the study include areas with the highest AD age-adjusted death rates; however, these areas have the lowest AD case rates, indicating the need for screening.

A key reason for this lack of screening includes lack of knowledge and misperceptions of primary care physicians on the consequences of undiagnosed and untreated AD. Continuing medical education training has been conceptualized for practitioners in target counties to enhance knowledge of cognitive impairment and dementia risk factors, screening and diagnosis, treatment, and available resources for patients and practitioners. Primary care physicians in target counties have been identified to contact to participate in the project.

The Community Health Worker (CHW) model is used to screen older adults; CHWs recruit older adults in their communities. CHWs are actively working in Alachua, Putnam and Union Counties, and recruitment is underway for CHWs in remaining counties. CHWs administer an intake to assess medical history as well as conduct an AD knowledge questionnaire and Montreal Cognitive Assessment (MoCA). Older adults who score less than 26 (highest score = 30) on the MoCA are referred to their primary care physician for further evaluation and possible referral to a memory disorder clinic. As of the end of September, HealthStreet has enrolled a total of 2,951 older adults, and this project contributed 112 older adults to the Florida AD registry and HealthStreet membership (Table 1). Among the 112 older adults enrolled in the project, 105 completed the AD questionnaire (HealthStreet total: 1,225), and 41 completed the MoCA (HealthStreet total: 311; Table 2). The average score on Alzheimer's disease knowledge is 9.4 out of 13. Twenty-four (24) older adults received a MoCA score less than 26, indicating the need for further assessment.

Dr. Cottler and her team continue to build both the Registry of Florida community dwelling older adults who may be interested in research participation and the statewide infrastructure to link older adults to cognitive screening and related health research through CHW recruitment, expanding network partnerships and training for cognitive impairment screening in nine Florida counties. The CHW model which includes information, education, connections to local community and medical services, and follow-up at 60 and 120 days has demonstrated an increase in AD knowledge by the older adults. This is an important finding as it provides the basis for additional interventions to improve AD-related health literacy. This project is increasing AD screening among older adults and providing education to physicians in rural areas to improve the identification of cases

**Follow On Funding:** None at the time of reporting.

**Collaborations:** This project is in collaboration with the following Departments and Colleges at the University of Florida: College of Public Health and Health Professions; College of Medicine in the Department of Epidemiology; College of Medicine for Continuing Medical Education; College of Medicine in the Department of Neurology; College of Journalism and Communications; and HealthStreet who are providing training to community health workers and partners.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

17. **Grant #8AZ18:** Investigations of Neuropathologies Targeted by Clinical Trials in Alzheimer's Disease Patients

**Principal Investigator:** Anthony T. Yachnis, MD

**Organization:** University of Florida

**Progress Report:** During the first quarter, organizational meetings were held and action items determined. The Institutional Review Board protocol was updated to reflect the award and comply with specific project requirements. The first study subject was enrolled in the study. During the second quarter, four additional subjects were enrolled. Three of these have been diagnosed with Alzheimer's disease (AD) while the fourth is diagnosed with MSA and will serve as a disease control. Three of these study subjects have come to autopsy. For these three, Dr. Yachnis and his team are working to identify additional information regarding the specifics of the clinical trial in which they were enrolled. These efforts from this quarter bring their total number of enrolled subjects to five. No additional subjects were enrolled during the third quarter. To address the lag in enrollment, they are working on preparing recruitment material to be approved by their local Institutional Review Board for distribution to clinics. The materials will be used to draw attention to their brain bank for distribution to patients within the Compass/Bioclinical trials program.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

18. **Grant #8AZ19:** Role of Microglia in Primary Age Related Tauopathy and in Sporadic (Late-Onset) Alzheimer's Disease

**Principal Investigator:** Wolfgang J. Streit, PhD

**Organization:** University of Florida

**Progress Report:** Processing of human brain tissue samples for immunohistochemistry and microscopic assessments of finished preparations are underway. Microglial cells are labeled immunohistochemically using the rabbit polyclonal primary antibody, ionized calcium binding adaptor molecule (Iba1), directed against the ionized calcium binding adaptor molecule 1 (Wako, 019-19741, diluted at 1:500). This antibody is known to bind to all microglial cells irrespective of their activation or degeneration state, and also works across several species.

Immunolabeling for the iron storage protein, ferritin, is performed using anti-ferritin polyclonal antibody (rabbit anti-horse spleen ferritin, Sigma, F6136, diluted at 1:800). Microglia/perivascular macrophages are labeled with an antibody against the intracytoplasmic lysosomal macrophage antigen, cluster of differentiation 68 (CD68) (monoclonal mouse anti-human CD68, Clone phosphoglucomutase 1 human recombinant (PG-M1), Dako Denmark A/S, M0876, diluted at 1:500). A monoclonal antibody against human PHF-tau, clone AT8 (mouse monoclonal, 1:2000, Thermo

Fisher Scientific, MN1020, diluted at 1:500), is used for detecting structures containing hyperphosphorylated tau protein (neuropil threads, pretangles, neurofibrillary tangles, and neuritic components of neuritic plaques). Amyloid-beta protein (A $\beta$ ) is detected using a monoclonal mouse antibody (clone NAB 228, Sigma, A8354, diluted at 1:5000). For immunostaining using peroxidase based procedures, sections are incubated free-floating in blocking buffer containing 10% goat serum, 0.1% Triton-X 100 in PBS for 1 h before applying the primary antibodies. Primary antibodies, diluted in PBS containing 5% goat serum and 0.1% Triton in PBS, are applied to sections and incubated overnight at 4 °C. After several washes, sections are incubated with either a biotinylated goat antimouse IgG (Sigma, B7264) or a biotinylated goat anti-rabbit IgG secondary antibody (Sigma, B8895), diluted 1:100, for 1 h at room temperature. Sections are then incubated with Avidin D conjugated to horseradish peroxidase (Vector, A-2004) and visualized using 3,3'-diaminobenzidine tetrahydrochloride (DAB) H<sub>2</sub>O<sub>2</sub> substrate (Sigmafast 3,3'-diaminobenzidine tablet sets, Sigma, D-4418). Selected sections are counterstained with hematoxylin after single immunostaining. Negative controls consist of omitting either the primary antibodies or incubating primary antibodies with mismatched secondary antibodies (e.g., primary mouse with biotinylated goat-anti-rabbit). All slides are dehydrated through ascending alcohols, cleared in xylene and cover slipped with Canada Balsam. Preparations are examined blindly (knowing only age, sex, and case number) and photographed using a Zeiss photomicroscope.

Thus far, microscopic evaluations of human brains from ten non-demented individuals show that each one of these subjects reveals some level of neurofibrillary degeneration, up to about Braak stage II. Only one of these individuals has shown presence of A $\beta$  deposits, and none of them have shown evidence of microglial activation (neuroinflammation). Microscopic evaluations will continue for the foreseeable future as preparations from more cases become available.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** This collaboration is between the University of Florida and the University of Leipzig, Germany. Both institutions are involved in postsecondary education of graduate and medical students. Currently, one graduate student and one medical student from the University of Leipzig are involved in this project.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

19. **Grant #8AZ20:** Seeded Interactions of Abeta; And Neurofibrillary Tangle Pathologies in Mouse Models

**Principal Investigator:** Guilian Xu, PhD

**Organization:** University of Florida

**Progress Report:** The purpose for this study is to find a way to make a better mouse models for Alzheimer's disease by seeding strategy. Alzheimer's disease is

characterized by abnormally accumulation of aggregated Abeta peptide and tau protein which form senile plaques and neurofibrillary tangles in the brain, respectively. Dr. Xu and associates plan to use 3 kinds of double transgenic mice (fast, medium and slow Abeta model cross to tau model) and inject different brain homogenates (made from transgenic mice overexpressing human Abeta, or human AD cases, plus test-tube formed aggregated tau) to speed up pathology of the animals. If they find a good combination to make a faster and reliable model, it can speed up the study of Alzheimer's disease in the lab and also better understand the mechanisms of the transmission of either Abeta or tau, which will direct impact to Floridians. During the last year, they requested 4 cases of frozen human brain tissues (3 AD cases and 1 healthy case) from Florida 1 Alzheimer's ADCR tissue bank to make homogenate for seeding. The research team made the Abeta mouse brain homogenates (107xtTA mouse, Bri42xtTA mouse) and K18 tau seeds in the lab. They are breeding 3 groups of animals, including PS19xCRDN8 (fast), PS19xL85 (medium) and PS19xMHSI-695 (slow). A few litters of animals from the above groups were born and the mouse brain homogenates have been injected into the new born pups. They also keep some uninjected pups and pups injected by PBS as negative controls. For the mouse brain homogenates injection, only about 20% of the mouse they planned to inject were born and injected. For the human brain homogenate injection, they are waiting for the tissue. So far, the team has harvested two litters of PS19xCRDN8 mice (uninjected mice and PBS injected controls) and did histology assay on them. The result is expected, but they only have one double transgenic mouse in these two litters. The time is in the early stage of the process waiting for the mice to be born, inject and age them. They are waiting for the human brain tissue. Once they receive them, they will make the homogenates and start to inject. Unexpected, PS19xCRDN8s very difficult to breed, the mouse number per litter is low (2-5 pups vs. normally 8-12 pups) and the females have poor motherhood behavioral, either ignore or eat pups. So far 7 litters have died. Except for the difficulty of the breeding of PS19xCRDN8 mice and the slow process to get the human brain tissues, there is no delay and the study is progressing as planned. There is no data to report at this time.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

20. **Grant #8AZ21:** Postdoctoral Fellowship In Neuropsychology

**Principal Investigator:** Rosie E. Curiel, PsyD

**Organization:** University of Miami Miller School of Medicine

**Abstract of Proposed Research:** The postdoctoral fellow in neuropsychology has been training on an expanding platform of patient-centered clinical research in the Center for Cognitive Neuroscience and Aging at the University of Miami Miller School of Medicine. Well-trained practitioner researchers skilled in the early detection of Alzheimer's disease and related disorders is critical for the expanding needs of the state of Florida and the nation as the population ages. The research fellow, Dr. Daema Piña is a bilingual and bicultural neuropsychologist and licensed psychologist. She evaluates older adult

individuals across their NIH and state-funded program that focuses on cognitive and functional decline in community-dwelling elders. Dr. Pina has assisted with grant and manuscript preparation, operational management, recruitment, developing and maintaining collaborations with multiple departments and community stakeholders, and learning to analyze data related to cognitive performance and biological markers of disease. She has done an excellent job thus far. Her training has spanned nearly two years (ending February 28, 2019), which will support her status as specialist in the field of neuropsychology and prepare her for a career in clinical research with older adults.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** The research fellow at the University of Miami Miller School of medicine teaches and supervises pre-doctoral practicum students that work on their research grants from two affiliated local institutions, Albizu University and Nova Southeastern University.

**Journals:**

Curiel, R.E., Crocco, E.A., Raffo, A., Guinjoan, S.M., et al. (2017). Failure to Recover from Proactive Semantic Interference Differentiates Amnesic Mild Cognitive Impairment and PreMCI from Normal Aging after Adjusting for Initial Learning Ability. *Current Alzheimer's Research*.

**Patents:** None at the time of reporting.

21. **Grant #8AZ22:** Cardiovascular and Lifestyle Stressors of Hippocampus and AD Related Brain Regions

**Principal Investigator:** Noam Alperin, PhD

**Organization:** University of Miami

**Progress Report:** Faced with aging global populations, the medical community has become increasingly interested in developing interventions to slow or prevent age-related dementia disorders like Alzheimer's disease. Sleep quality has been targeted as a factor that may help modulate the course of amnesic mild cognitive impairment and Alzheimer's, but the relationship between sleep and dementia disorders is still poorly understood. Dr. Alperin's study reports that patterns of cortical and deep gray matter atrophy related to poor sleep quality impact Alzheimer's disease-related regions of the cortex even in a population rigorously deemed *unaffected by cognitive impairment*, psychological disorders, or dementia. The study emphasizes a role for sleep intervention in fighting neurodegeneration of Alzheimer's-related brain regions.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Alperin N, Wiltshire J, Sang L. (2018). Effect of Sleep Quality on aMCI Vulnerable Brain Regions in Cognitively Normal Elderly Individuals. *SLEEP*, (in press) (pending administrative review).

**Patents:** None at the time of reporting.

22. **Grant #8AZ23:** The Relationships Between Multimodal Neuroimaging Biomarkers and a Novel Cognitive Stress Test (CST) Among Ethnically Diverse Older Adults

**Principal Investigator:** David Loewenstein, PhD

**Organization:** University of Miami Miller School of Medicine

**Progress Report:** This application awarded in 2018 proposes a unique consortium between top investigators from the University of Miami, University of Florida, Florida International University and Mount Sinai Medical Center generating an unprecedented opportunity to evaluate a) a newly developed novel, computerized cognitive stress test (CST) developed to identify unique cognitive markers of early Alzheimer's disease among diverse ethnic and cultural groups (African-American, Hispanic and White-Non-Hispanic) at risk for Alzheimer's disease; b) employing study state-of-the-art multi-modal neuroimaging (tau, amyloid load, cortical thickness, regional brain volumes and DTI).

This consortium of talented investigators will be the first in the State of Florida to examine the relationship between a new more powerful computerized cognitive test (CST), tau and amyloid load in the brain as they relate to novel cognitive stress tests that have been found to be extremely sensitive markers of PreClinical AD by uniquely tapping susceptibility to proactive semantic interference (PSI) and failure to recover from PSI (frPSI), and now uniquely, deficits in failure to recover from retroactive semantic interference frPSI. The consortium will leverage existing resources and data provided by the 1Florida ADRC and the University of Miami's longitudinal NIH study on aging and cognition (Dr. Loewenstein, PI) and will recruit additional minority older adults at risk for early AD.

Dr. Loewenstein's collaborative team provides special expertise in quantitative multimodal neuroimaging, diagnosis of early cognitive impairment (MCI and PreMCI states), and the development of novel cognitive stress paradigms that are cross-culturally sensitive. This collaborative study is high impact in that it expands upon and further refines diagnostic strategies for early detection of PreClinical AD and emerging treatments. It will also yield important and critical pilot data for successful collaborative R01 and other federal grant submissions to the National Institutes of Health.

They have made significant progress on this study. The computerized cognitive stress tests (CST) has been developed and implemented and now is being administered to both those with amnesic Mild Cognitive impairment (aMCI), those who have PreMCI and cognitively normal individuals representing diverse ethnic and cultural backgrounds. They just signed contract with Piramel Life Sciences that will allow them to commence tau imaging on a subset of 30 participants and will represent the first attempt in the country to relate CST performance to tau imaging in the brain, not just in Florida but in the United States. The advanced computerized stress test and their use of tau biomarkers will represent a significant advance in developing cognitive stress tests that will likely have important implications early detection of AD and methods of evaluating novel and emerging therapeutic implications.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** Dr. Stephen Dekosky from the University of Florida who is working on Tau and Amyloid Neuroimaging; Dr. Maria Grieg from Mount Sinai Medical Center working on Cross-Cultural Diagnosis of Early AD; and Dr. Makek Adjouadi from Florida International University who is working at the Cate Center for Neuroimaging.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

23. **Grant #8AZ24:** Extracellular Vesicles as Novel Therapeutic Targets in Alzheimer's Disease

**Principal Investigator:** Michal Toborek, MD, PhD

**Organization:** University of Miami

**Progress Report:** Virtually all cells of the human body shed vesicles into the extracellular space, which then travel via the blood stream and can reach distant organs. These vesicles, named "extracellular vesicles" (ECV), carry content characteristic to the cells they originate from, including a protein called amyloid beta (Abeta). Deposits of Abeta in the brain have been linked to the memory loss and cognitive decline in individuals suffering from Alzheimer's disease (AD). Dr. Toborek and associates propose that ECV can bring Abeta from the periphery into the brain by crossing the blood-brain barrier (BBB), a critical interface built by small brain vessels that normally protects the brain from the majority of blood-borne factors.

The mechanistic link between elevated deposits of Abeta in the brain and loss of memory in AD is not fully understood. However, it is important to note that neural progenitor cells (NPC), i.e., cells that produce new neurons even in the adult brain, are located in close proximity to brain microvessels forming the BBB. NPC-derived neurons are critically important for normal brain function because they are built into normal neuronal networks and participate in memory formation.

Their proposal explores the role of ECV in Abeta transfer to NPC and the outcomes of this process, such as impaired production of new neurons, resulting in memory loss. By better understanding of these events, they will be able to provide novel therapeutic targets in AD. Thus, the proposal is highly significant to Floridians suffering from AD and/or their families. If successfully completed, their research will constitute an excellent return on investment.

The progress on this project includes development and standardization of several critically important model systems that allow to evaluate the formation and trafficking of ECV, and transfer of Abeta to different cell types. Importantly, they are now able to monitor transfer of ECV and their cargo into the brain by visualizing not only ECV but also brain vessels.

Overall, their proposal offers a unique perspective on the interactions between the BBB, ECV, and Abeta deposits, resulting in impaired formation of new neurons in adult brain.

They expect that therapeutic targeting of this process can protect against Abeta pathology and memory loss in AD.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

24. **Grant #8AZ25:** Identification of Noncoding Functional Variant(s) Underlying Alzheimer Disease GWAS Hits

**Principal Investigator:** Anthony Griswold, PhD

**Organization:** University of Miami

**Progress Report:** Alzheimer's disease (AD) is the most common neurodegenerative disease and the leading cause of dementia with ~510,000 individuals in Florida (nearly 12% of Florida's senior population) and approximately 5.4 million individuals in the US across all racial and socio-economic strata. Current and emerging AD therapies focus on treating clinical symptoms, not the underlying pathological mechanisms of disease; largely because the field's understanding of these mechanisms is still limited. In an era of personalized medicine where one's disorder will be treated based not just on specific clinical symptoms but underlying genetic information, it is imperative the genetics field makes a concerted effort to understand the biological mechanisms in which genetic (risk) factors exert their effect.

Genome wide association studies (GWAS) have identified at least 20 genetic markers associated with Alzheimer disease (AD). The vast majority of associated GWAS variants (~77%) in complex diseases are located in non-protein coding regions of the genome with potential regulatory function (Maurano et al., 2012). Identification of the functional variant contributing to risk in noncoding regions is complex. First, since single nucleotide polymorphisms (SNPs) in association studies are part of large linkage disequilibrium (LD) blocks containing multiple SNPs, the top associated SNP may not be the 'driver' variant, rather any of the variants in LD with the top SNP could be the variant driving the association. Second, the regulatory elements (RE) including promoters, enhancers/silencers and insulators can affect genes located a significant distance away depending on 3D conformation of the chromosome. Taken together, the gene nearest to the top SNP may not be the gene whose affected expression is increasing risk for AD, complicating interpretation of GWAS results.

This proposal aims to identify the functional variant(s) driving the association in the PICALM locus with AD. Studies in different racial and ethnic population groups have found evidence for association with AD in white/non-Hispanic, African American and Hispanic datasets (Naj et al., 2011; Lee et al., 2011; Logue et al., 2011). However, sequencing of the coding region of PICALM have not identified coding variants of great

effect. Toward understanding the role of variants in the PICALM locus in regulating downstream mechanisms, their research team has thus utilized extensive in-silico bioinformatics analysis to annotate more than 20,000 variants identified across diverse populations in genome sequencing studies. Dr. Griswold and associates are in the process of utilizing this information to design a massive parallel reporter assay (MPRA) that will identify candidate variants that can regulate gene expression. The future of this project will use genome-editing technology combined with RNAseq and AD phenotype analysis to determine the effects of these variants. The development of an in-house MPRA protocol will be widely applicable, not only to the phosphatidylinositol binding clathrin assembly protein (PICALM) locus, but to other noncoding regions reported to be contributing to AD and by extension other neurodegenerative disorders.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

25. **Grant #8AZ26:** Investigating the Role of SORL1 in Alzheimer's Disease

**Principal Investigator:** Derek Dykxhoorn, PhD

**Organization:** University of Miami

**Progress Report:** Alzheimer's disease (AD) is the leading cause of dementia among the elderly affecting ~500,000 Floridians. This disease places a significant social and economic burden on families and the healthcare system. Genetics studies over the past decades have identified a variety of AD-associated genes. How many these genes contribute to the development of AD is a point of ongoing research. This proposal seeks to understand the role that variation in the Sortilin Related Receptor 1 (*SORL1*) gene plays in AD pathogenesis. The *SORL1* gene is able to function as a transmembrane signaling receptor and can bind low density lipoproteins, as well as, playing a role in endocytosis and intracellular sorting. Given the importance of intracellular trafficking in the proper process of amyloid precursor protein (APP), a key protein in the pathology of AD, Dr. Dykxhoorn and associates hypothesize that variants in *SORL1* will affect the production of pathogenic cleavage products of APP.

Their researchers had previously identified a novel single nucleotide deletion causing a premature stop codon in a family with early onset AD. Induced pluripotent stem cells (iPSC) have been generated from whole blood collected from members of this family. These iPSC were shown to be heterozygous for the single nucleotide deletion. To understand the role of this deletion on AD pathogenesis, they propose to correct the mutation in the iPSC lines which bear the mutation and add the mutation to lines which lack the mutation using genome editing technologies. This will allow for the determination of both the role of *SORL1* in AD pathology and establish whether variants in the *SORL1* gene are sufficient to induce AD-associated phenotypes. Since the award

of this grant, all the necessary regulatory documents, including the human subjects and recombinant DNA, have been obtained. The iPSC lines generated have been expanded and the differentiation protocol to produce cortical neurons has been initiated. In addition, the short guide RNAs that will be used for the genome editing approaches have been generated for both the correction of the AD-associated deletion and the introduction of this deletion into control, unaffected iPSC lines. These vectors are currently being tested in human cell lines to identify those which have the most potent targeting of the correct site in the SORL1 gene. Once the effective guide RNAs have been identified, they will be used to treat the appropriate iPSC lines. These genome edited cell lines will be differentiated into cortical neurons for analysis of AD-associated cellular phenotypes, understanding the role that the SORL1 gene plays in AD pathogenesis will elucidate the molecular mechanisms that underlie AD and help in developing more effective strategies to treat this common and debilitating disease.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

26. **Grant #8AZ27:** Emerging Role of Tau Citrullination in Alzheimer's Disease

**Principal Investigator:** Maj-Linda B. Selenica, PhD

**Organization:** University of South Florida

**Progress Report:** Alzheimer's disease (AD) is a devastating disease that impacts the life of over 5 million Americans living with the disease and their caregivers. To date AD stands alone as the only disorder that cannot be prevented, slowed, or cured, speaking to the complexity of the disease. Its pathology consists of amyloid beta and tau pathology, neuronal loss and ultimate cognitive decline. Brain inflammation is a crucial feature of AD pathogenesis. The challenge is to find therapeutic solutions that target multiple pathologies. This study is being done to describe a novel and irreversible post-translation modification of tau that has implication in its pathology and inflammation. Researchers have demonstrated breakage of blood brain barrier (BBB) and infiltration of circulating immune cells in the brain of AD-like animal models, suggesting a role of these cells in neuroinflammation. BBB can recover integrity when tau levels are reduced and immunotherapy against tau reduces both pathology and neuroinflammation. Recently, the infiltration of a subset of circulating immune cells (neutrophils) has been shown in AD brains. Neutrophils are responsible for a phenomenon known as neutrophil extracellular traps (NETs), individuals with AD, suggesting that these formations may induce neuroinflammation processes and promote pathogenesis. Peptidylarginine deiminase (PAD) enzymes carry out citrullination of arginine residues by replacing the positive charge to neutral citrulline. This modification can have significant consequences on

protein structure and function. Importantly, peptidylarginine deiminase 4 (PAD4) is essential for the production of NETs.

Dr. Selenica's team has identified a significant increase in protein levels of peptidylarginine deiminases (PAD2) and 4 in the brains of animal models of tauopathies, suggesting that tau pathology induce citrullination and NET formation. They also find increase PAD4 gene transcripts in the brains of AD compared to control patients. Importantly, they are the first to identify several putative citrullinated sites on tau by PAD4, two of which confirmed the novel antibodies in animal models of know how tau citrullination by PAD4, two of which confirmed the novel antibodies in animal models of tauopathology. Altogether, it suggests that tau pathology induces PAD4 and in vivo citrullination of tau. It is not known how tau citrullination by PADs impacts its fate. Their objective is to determine if PAD4 overexpression promotes tau citrullination and exacerbates tau aggregation in an animal model of tauopathy. They plan to 1) induce expression of PAD4 via adeno-associated virus and determine the extent to tau citrullination, 2) drug-induced PAD4 expression and NETs formation in the periphery of tau transgenic mice to determine if myeloid-induce PAD4 expression and NETs formation in the brain 3) measure several components of the tau phenotype, previously established in their laboratory. Additionally, they will determine if immunization of transgenic has not been described before, the success of this study will provide new knowledge in the AD field. More importantly, it will provide novel tools and potential biomarkers for developing translational strategies with direct outcome on the pathogenesis of this devastating disease.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

27. **Grant #8AZ28:** Microglial Phenotype in Alzheimer's Disease.

**Principal Investigator:** Kevin Nash, PhD

**Organization:** University of South Florida

**Progress Report:** This project is currently on going. The basic design is twofold, 1) determine how the immune cells are reacting to the disease pathology and 2) how the inflammation protein fractalkine can alter the immune cells in a positive way to reduce neuron loss.

Some of the initial period was spent in breeding up the mouse colony. This is rather an involved process which requires the breeding of two different mouse lines that Dr. Nash and his team then have to cross with each other to generate the Alzheimer mice. These mice are then aged 6 months in order to develop the disease pathology needed. During this time, Dr. Nash and his team have also established and optimized their isolation of

immune cells from mice brains. This using an antibody that specifically recognizes the immune cells and allows the researchers to isolate them from all the other cell types in the brain. They are going to assess the immune cells by looking at which genes are active under their different conditions. This involves looking at the RNA profile, or the transcriptome of those cells. Therefore, they also established their method of isolation of RNA from the immune cells.

They currently have isolated immune cells from their first group of normal animals and animals with disease pathology and have sent off the ribonucleic acid (RNA) to begin profiling. More animals are currently aging to increase the number of animals needed.

In order to examine the second part of their study they need to increase the protein Fractalkine in the disease mouse brain. For this, the team will use a gene therapy approach. They have generated and purified a virus that can deliver the fractalkine gene to the mouse brain. The first group of animals have been injected and are breeding. Additionally, more animals are being aged for this study as well. The team will be comparing animals treated with the fractalkine, compared to those that are not treated.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

28. **Grant #8AZ29:** Divergent RanBP9 Signaling in Tau Pathogenesis

**Principal Investigator:** David E. Kang, PhD & Jung A. Woo

**Organization:** University of South Florida

**Progress Report:** Alzheimer's disease (AD) is a devastating neurodegenerative dementia associated with Abeta and tau pathologies in brain that currently afflicts 5.4 million individuals in the United States and close to 500,000 in the state of Florida. Due to the aging population, the number of United States overall is estimated to rise to 13.2 million by 2050 if no effective treatment is found. In Florida, it is estimated that individuals living with AD is rising 20% every 10 years, thereby reaching a number close to 1.2 million by the year 2050. In 2012, the cost of caring for AD and related dementia patients in the United States stood at \$200 billion/year, and this figure is projected to rise to \$1.1 trillion/year by 2050 (2012 dollars). Therefore, AD is tremendous cost greater than the cost of doing research to prevent or slow the progression of AD. The major hypothesis of AD is the Abeta/amyloid hypothesis, which states that the accumulation of pathology and associated neuronal degeneration. Indeed, this hypothesis is widely supported by multiple generic, biochemical and cell biological studies. However, it is also clear that tau is required for Abeta/amyloid to transmit its neurotoxic signals, and accumulation of tau *per se* is neurotoxic. Therefore, understanding the molecular mechanisms that regulate the production of Abeta and how neurotoxic signals are

transmitted to tau are critical for discovering novel and promising therapeutic strategies to combat AD. Thus far, no disease-modifying drug has yet to show efficacy in moderate to severe cases of AD, perhaps because a therapeutic strategy may need to treat both ongoing Abeta production and block the neurotoxic signals between existing Abeta and tau pathologies.

The molecular pathway under investigation (RanBP9 & cofilin) regulates both new Abeta production and Abeta/amyloid-induced tau pathogenesis. Dr. Kang's findings indicate that RanBP9 not only activates cofilin to deregulate chaperones Hsp90 and Hsc70. This proposal seeks to understand how Ran-binding protein 9 (RanBP9) together with heat shock protein 90 (Hsp90)/heat shock cognate 71 kDA protein (Hsc70) regulate tau aggregation and microtubule dynamics as well as investigate whether activated cofilin (but not inactive cofilin) promotes tau pathology in brain. Both aims have profound implications for AD therapeutics, as Hsp90/Hsc70 and cofilin activation are molecular therapeutic targets for AD under active development. Their findings thus far indicate that the RanBP9 molecule positively regulates tau levels, which is one hallmark of AD pathology. They are currently testing whether RanBP9 also promotes tau aggregation or clumping together. Finally, they are also testing whether the 'activate' form of cofilin versus the 'inactive' form selectively promotes tau pathology in brain. This question has important therapeutic implications, as controlling the 'activation' of cofilin can be done using chemical inhibitors to an enzyme called slingshot protein phosphatase 1 (SSH1), which they are currently developing.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** This project is collaborating with graduate student Yan Yan at USF Health located at the University of South Florida.

**Journals:**

Woo, J.A\*, Liu, T., Fang, C., Cazzaro, S., (2018). *Activated cofilin in tau-mediated microtubule dynamics and tauopathy*. Under revision in Communications Biology

**Patents:** None at the time of reporting.

29. **Grant #8AZ30:** Exploiting GPRC6a Antagonists to Mitigate Tau Deposition

**Principal Investigator:** Daniel C. Lee, PhD

**Organization:** University of South Florida

**Progress Report:** Currently no accurate measure for the number of neurodegenerative diseases exists but estimates suggest greater than 600 brain disorders exist impacting 100 million Americans and costing more than \$5billion according to NIH. More than 20 different tauopathies including Alzheimer's disease (AD) exist with increasing behavioral phenotypes presenting in the clinic. Tau correlates most closely to neurodegeneration when assessing various aspects of the AD pathology. Arginine metabolism remains important for numerous cell pathways and seemingly shows considerable influence upon tau biology. At least 5 different enzymes metabolize arginine, thus sensing extracellular

abundance of arginine remains critical for cell survival. G Protein-coupled receptor class C group 6 Member A (GPRC6a) is a G-protein coupled receptor that binds with high affinity to arginine. Dr. Lee and his team postulate that GPRC6a regulates autophagy. The team hypothesizes that decreased signaling of GPRC6a via gene therapy or pharmacologically activates autophagy and tau clearance. They posit that GPRC6a remains tonically activated and senses extracellular amino acid abundance of basic L-alpha amino acids specifically L-arginine during neurodegenerative conditions. Herein, they will elucidate a mechanism by which GPRC6a modifies tau metabolism using several approaches: genetic repression of GPRC6a and novel pharmacological GPRC6a antagonists. Success in this application would provide a new receptor function that may govern autophagy through amino acid sensing and is predicted to prevent the tau phenotype. The multidisciplinary approach of basic science, and pre-clinical validation in animal models of tauopathy provides a global approach. Furthermore, they gain a new class of drugs (allosteric antagonist of GPRC6a) that could become new therapeutics for tauopathies and other neurodegenerative disease. They have currently optimized their tau degradation assay using a photo-convertible fusion protein linked to tau. This assay permits them to measure tau synthesis and clearance in real time in relation to drug therapies. Additionally, they have identified that their lead compound to GPRC6a and two more selective GPRC6a inhibitors that increase tau clearance. The two more selective compounds increase tau clearance a better rate than the lead compound. Their next step will be to utilize a secondary assay for tau clearance and begin to test the best candidate drugs in vivo.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

30. **Grant #8AZ32:** Longitudinal Assessment of BDNF Levels with Bacopa Monnieri Treatment in those at Risk of Developing Alzheimer's Dementia

**Principal Investigator:** Andrew Keegan, MD

**Organization:** The Roskamp Institute

**Progress Report:** This two-year project began in March of this year with the first component. The goal of this first portion is to evaluate how a population of subjects who are at risk for developing Alzheimer's disease (based on age) have changes in levels of a factor important for maintaining neurons and their connections called Brain Derived Neurotrophic Factor (BDNF). The research staff were first trained on the protocol and subsequently collection of the first samples occurred in April of this year. Over subsequent months, research staff continued to collect blood samples and memory tests for those subjects participating in the study. Research staff are meeting grant goals collecting adequate numbers of subject samples and placing them in storage for the

second year when they will be analyzed. The collection of samples for this first component will be completed in April of 2019.

For the second component of the study, a group of subjects will be supplied a supplement (Bacopa) over a 3-month period and changes in Brain Derived Neurotrophic Factor (BDNF) will be assessed. Staff is preparing that protocol for submission to the IRB to start that portion of the study in early 2019 to stay on track for lab evaluation of the samples towards the end of 2019. These will be local Floridians participating in the study that may provide preliminary data on the potential benefits of this supplement on cognitive aging.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

**APPENDIX C**  
**FISCAL YEAR 2017-2018 ACTIVE GRANTS**  
(Funding Year 2016-2017)

Grant #	Organization	Principal Investigator	Award Amount	Life To Date Expenditure	Unspent Funds	Executed Date	End Date	Patents	Publications	Follow-on Funding
7AZ01	University of Florida	Smith, Glenn	\$ 450,000	\$ 350,000	\$ 100,000	2/01/2017	3/31/2019	No	Yes	Yes
7AZ02	Florida International University	Burke, Shanna	\$ 99,994	\$ 77,770	\$ 22,224	2/01/2017	3/31/2019	No	No	No
7AZ03	University of South Florida	Kang, David	\$ 250,000	\$ 194,446	\$ 55,554	1/26/2017	3/31/2019	No	Yes	No
7AZ04	University of Miami	Rotundo, Richard	\$ 250,000	\$ 194,446	\$ 55,554	2/01/2017	3/31/2019	No	No	No
7AZ05	Mayo Clinic Jacksonville	McLean, Pamela	\$ 250,000	\$ 194,446	\$ 55,554	2/02/2017	3/31/2019	No	No	No
7AZ06	University of Florida	Bizon, Jennifer	\$ 100,000	\$ 77,777	\$ 22,223	1/25/2017	3/31/2019	No	No	Yes
7AZ08	Mayo Clinic Jacksonville	Dickson, Dennis	\$ 100,000	\$ 66,666	\$ 33,334	2/01/2017	3/31/2019	No	Yes	Yes
7AZ11	University of Central Florida	Sugaya, Kiminobu	\$ 100,000	\$ 41,174	\$ 58,826	2/06/2017	3/31/2021	No	Yes	No
7AZ12	University of Florida	Rincon-Limas, Diego	\$ 249,998	\$ 222,224	\$ 27,774	2/06/2017	3/31/2019	No	No	No
7AZ13	University of South Florida	Gulick, Danielle	\$ 100,000	\$ 76,666	\$ 23,334	2/14/2017	3/31/2019	No	No	No
7AZ14	University of Miami	Curiel, Rosie	\$ 249,846	\$ 189,794	\$ 60,052	2/23/2017	3/31/2019	No	No	Yes
7AZ17	Mayo Clinic Jacksonville	Ertekin-Taner, Nilufer	\$ 308,807	\$ 202,441	\$ 106,366	2/06/2017	3/31/2019	No	Yes	No
7AZ18	University of Miami	Loewenstein, David	\$ 249,980	\$ 166,256	\$ 83,724	2/27/2017	3/31/2019	No	No	No

7AZ19	University of Florida	Levites, Yona	\$ 250,000	\$ 194,446	\$ 55,554	2/01/2017	3/31/2019	Yes	Yes	No
7AZ20	University of Miami	Cukier, Holly	\$ 250,000	\$ 194,446	\$ 55,554	2/01/2017	3/31/2019	No	No	No
7AZ21	Mayo Clinic Jacksonville	Cook, Casey	\$ 250,000	\$ 134,617	\$ 115,383	2/01/2017	3/31/2020	No	No	No
7AZ22	Mayo Clinic Jacksonville	Kanekiyo, Takahisa	\$ 250,000	\$ 102,942	\$ 147,058	2/01/2017	3/31/2021	No	Yes	No
7AZ23	University of South Florida	Cheng, Feng	\$ 98,449	\$ 75,110	\$ 23,339	2/01/2017	3/31/2019	No	No	No
7AZ24	University of South Florida	Gamsby, Joshua	\$ 100,000	\$ 69,940	\$ 30,060	2/01/2017	3/31/2019	No	Yes	No
7AZ25	University of Florida	Giasson, Benoit	\$ 250,000	\$ 172,990	\$ 77,010	2/01/2017	3/31/2019	No	Yes	No
7AZ26	University of Miami	Wahlestedt, Claes	\$ 100,000	\$ 41,174	\$ 58,826	2/01/2017	3/31/2021	No	No	No
7AZ27	University of Central Florida	Tatulian, Suren	\$ 100,000	\$ 54,323	\$ 45,677	2/01/2017	3/31/2020	No	No	No
7AZ28	Florida Atlantic University	Wiese, Lisa	\$ 95,133	\$ 62,220	\$ 32,913	5/15/2017	6/30/2019	No	Yes	No

**Active Grants Fiscal Year 2018-2019**  
(Funding Year 2016-2017)

1. **Grant #7AZ01:** Physical Exercise and Cognitive Engagement Outcomes for Mild Neurocognitive Disorder (PEACEOFMND)

**Principal Investigator:** Glenn Smith, PhD

**Organization:** University of Florida

**Progress Report:** In August the University of Florida (UF) conducted another session with four new couples. In July Mayo conducted a follow-up and in August Tallahassee Memorial Hospital (TMH) conducted follow-up, both with participants from their second sessions. Dr. Smith and associates currently have 43 (15 by Mayo, 16 by UF and 12 by TMH) participants enrolled with four more recruited for August at UF. Three additional couples enrolled in the program but dropped out before completing the six-month program. TMH recruited Ailyn Penate PhD to replace Dr. Bhasker and she has agreed to be involved with the study. They are looking to run another session after the first of the year. UF will conduct a fifth session in December and they currently have seven participants enrolled.

**Follow On Funding:** Alzheimer's Association, Clinical Fellowship to Promote Diversity  
Total Funds Awarded: \$150,000.00

**Collaborations:** The Department of Clinical and Health Psychology at the University of Florida is the primary site for this project. Graduate students (pursuing PhDs in clinical psychology) are very involved in the program. Four graduate students and three undergraduate members of the PI's (Glenn Smith) lab have been involved in obtaining IRB approval, patient recruitment, screening data collection. Additional UF grad students have been trained in and delivered the intervention. Dr. Levy and a graduate student at UF are using the project as a basis to study barriers to participation in African American communities. A post-doctoral fellow of Dr. Chandler's is involved with the project at Mayo Jacksonville (Department of Psychiatry and Psychology) and received a grant to adapt the program for Spanish-speakers.

**Journals:**

De Wit, L., O'Shea, D., Chandler, M.J., Bhaskar, T., Smith, G., et al. (2018). Physical Exercise And Cognitive Engagement Outcomes For Mild Neurocognitive Disorder: a group-randomized, recruitment and outcome assessor blinded trial. *BMC Trials*. 19, 573, doi: <https://doi.org/10.1186/s13063-018-2865-3>

**Patents:** None at the time of reporting.

2. **Grant #7AZ02:** Demographic, Neuropsychological and Functional Classification, Risk Factors, and Progression Rates of Individuals Diagnosed as "Impaired Not MCI" in the National Alzheimer's Coordinating Center Database Using Algorithmic Diagnosis

**Principal Investigator:** Shanna L. Burke, PhD

**Organization:** Florida International University

**Progress Report:** The National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) was utilized as the algorithm training dataset as it contained data from 35 past and present Alzheimer's Disease Centers from 2005 to 2017, 118,341 participant visits and 35,183 unique participants. To determine variable inputs, Dr. Burke and associates tested the ability of Clinical Dementia Rating Sum of Boxes (CDRsb) scores to distinguish between adjacent cognitive impairment diagnoses versus four different combinations of neuropsychological tests. They determined the optimal cut-off point of CDRsb that maximized the sensitivity and specificity of the Receiver Operating Characteristic (ROC) curve, and applied the cut-off point to the validation sample to obtain the predicted diagnoses. Using the information derived from the ROC analyses, they then codified the algorithm based on the Duara et al., (2010) consensus diagnosis algorithm using Python software. For creating digital inputs to the algorithm, they utilized the CDRsb and diagnosis variables from the NACC data set. They called the resulting algorithm the (eAlgDx). In all, there are 294 possible permutations of the eAlgDx algorithm.

**Results:** The optimal cut off point maximizing the sensitivity and specificity was normal vs MCI: 0.25 and for Mild Cognitive Impairment (MCI) vs Alzheimer's disease (AD): 3.25. This means CDRsb score of 0 is equivalent to normal cognition, and a CDRsb score between 0.5 and 3 is indicative of MCI, and a CDRsb score between 3.5 and 18 indicates AD. The level of agreement between the original NACC diagnoses and the eAlgDx was low which was expected. They anticipated that the algorithm would be more sensitive to the newly established cutoffs and be able to further subdivide the cases that were normal, impaired not MCI, MCI, and demented as indicated in the original dataset. The research team repeated the ROC analyses using the eAlgDx to explore how well it distinguishes the adjacent diagnostic categories, which was previously conducted in the raw data. For example, they found that of the 78,401 visits previously classified as impaired not MCI, only 5,636 cases remained as impaired not MCI, and others were reclassified in a more precise manner. The eAlgDx algorithm was able to reclassify 72,765 visits as dementia (31,073), MCI (20,498) or normal (21,194) using the newly established cutoffs. Furthermore, they analyzed 7228 visit results, which were originally classified as MCI. The new sensitivity of the eAlgDx reclassified these into 169 occurrences of dementia, 3180 occurrences of MCI and 3879 occurrences of normal cognitive status.

The team has begun drafting the first manuscript disseminating their results. The researchers presented their findings from Aims 1 and 2 at the Florida Health Alzheimer's Disease Research and Awareness Symposium, Orlando, FL. On June 8, 2018. In the first week of August, the PI met with investigators in Chicago, IL to discuss risk and protective factors for longevity and neurodegeneration, which could be included in the algorithm in Aim 2 (BMI, caloric intake, cardiovascular risk factors, and genetics). In November, they will present their results in an oral presentation at the Gerontological Society of America scientific meeting in Boston, MA. The key personnel and scientific programs and the project has benefited from the collaboration between UF and FIU, and consulting from Dr. Loewenstein of the University of Miami.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** This project is collaborating with the Florida International University (Drs. Shanna Burke, Tianyan Hu, Wensong Wu, and Ingrid Gonzalez); the University of

Florida (Drs. Christopher Barnes and Kevin Hanson); and the University of Miami (Dr. David Loewenstein).

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

3. **Grant #7AZ03:** Structure Activity Characterization of Novel Slingshot Inhibitors

**Principal Investigator:** David Kang, PhD

**Organization:** University of South Florida

**Progress Report:** Alzheimer's disease (AD) is a devastating neurodegenerative disorder of the brain that afflicts more than 5.4 million people in the United States and close to 500,000 people in Florida. At present however, there are no effective treatments or therapeutics for AD. Two major pathologies – namely amyloid plaques and Tau tangles – are largely responsible for the neurodegenerative changes seen in AD brains. While amyloid pathology is thought to initiate AD pathogenesis, Tau is essential to execute the progressive neurodegeneration seen in AD. Dr. Kang's studies have found that amyloid activates Slingshot-1, an enzyme that activates Cofilin, while Cofilin is over-activated in brains of AD patients. Activated Cofilin is known to induce the breakdown of neuronal connections in brain and impair energy production within neurons. Their preliminary studies have also implicated activated Cofilin in the enhancement of AD pathological measures (amyloid & pathological tau). Therefore, partially inhibiting the enzymatic activity of Slingshot-1 may provide therapeutic value to halt or slow the progression of AD at multiple levels.

Dr. Kang's team utilized the Chembridge Central Nervous System (CNS)-Set compound library to screen for Slingshot modulators using a 3-step screening approach. The CNS-Set consists of drug-like compounds selected for increased probability of oral bioavailability and blood-brain-barrier penetration. As a part of this funded project, they first carried out virtual pre-docking of the >50,000 CNS-Set library against the X-ray crystal structure of Slingshot catalytic core to narrow down the top 10 percentile that are mostly likely to exhibit activity. In the second step, they carried out physical screening for Slingshot inhibitors using purified Slingshot-1. They identified a series of compounds called the 'C' series that exhibited promising Slingshot inhibitory activity. They have focused on the C2 compound and synthesized several derivatives. Some of these modified series of compounds exhibited higher potency in Slingshot inhibition as well as in reducing pathological tau. Their goal is to further develop these C2 derivatives, test them for specificity, and eventually for efficacy in animal models. They are also developing other derivative compounds based on C2 and C1 compounds to identify even higher potency compounds.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** This project is collaborating with USF Health: Kang, Chen, Leahy labs.

**Journals:**

Liu, T., Wang, F., LePchat, P., Woo, J.A, Kang, D., et al. (2017). Cofilin mediated neuronal apoptosis via p53 translocation and PLD1 regulation. *Scientific Reports*. 14;7(1):11532. doi:10.1038/s41598-017-09996-3. PMID: PMC5599510

**Patents:** None at the time of reporting.

4. **Grant #7AZ04:** Enhanced Acetylcholinesterase Expression Induced by Donepezil and Galantamine

**Principal Investigator:** Richard L. Rotundo, PhD

**Organization:** University of Miami Miller School of Medicine

**Progress Report:** Acetylcholinesterase is the enzyme that terminates neurotransmission by cholinergic neurons in the brain, some of the most important ones for memory and learning. Alzheimer's disease includes loss of these neurons. The most important drugs for treating patients with Alzheimer's disease are acetylcholinesterase (AChE) inhibitors including Donepezil (Aricept) and Galantamine (Reminyl). Dr. Rotundo and his team discovered in preliminary studies that these drugs also can act as chaperones, molecules that help proteins fold correctly, and as a consequence they can also increase AChE activity in the brain. That's the opposite effect that they want from these drugs and so they are trying to develop other ways of inhibiting AChE without increasing the enzyme.

Their work for the past year has focused on studying the folding of AChE in tissue cultured cells as a model system, and then also in vivo using a mouse model. They showed that the AChE inhibitors, Donepezil and Galantamine, dramatically increase AChE activity by themselves in addition to their conventional role of inhibiting the enzyme. However, another type of AChE inhibitor called Rivastigmine (Exelon) can inhibit the enzyme as well as the others but does not enhance the folding of the protein and thus does not increase AChE activity. Their studies suggest that perhaps a mixture of these two types of AChE inhibitors might be a better therapeutic solution than one alone.

Additional studies this past year from their lab have shown that specifically the cholinergic synapses are being affected, precisely the same ones that degenerate in Alzheimer's disease, strengthening their hypothesis that this over expression of the enzyme can be detrimental to drug treatment. The researchers' results will impact treatment of Alzheimer's patients in Florida and all over because they will lead to improved drug therapy. In addition, their results may help explain why many patients do not respond to anticholinesterase drug therapy and may increase the effectiveness of current therapies. These exciting results were presented at the annual Society for Neuroscience meeting, November 3-7, 2018.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

5. **Grant #7AZ05:** How Does Alpha-Synuclein Contribute to Tau Dysfunction in Alzheimer's Disease?

**Principal Investigator:** Pamela McLean, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** The goal of this proposal is to identify any previously unidentified alpha-synuclein pathology and alpha-synuclein-tau interactions in post-mortem Alzheimer's disease (AD) brain with a view to determining if alpha-synuclein plays a role in AD pathogenesis and if alpha-synuclein/tau crosstalk contributes to AD progression.

Alpha-synuclein is a small protein that accumulates in the brains of persons with Parkinson's disease. However, a significant number of AD patients are found to have alpha-synuclein pathology in their brains at post-mortem. In addition, alpha-synuclein is reported to interact with tau protein, which accumulates as neurofibrillary tangles in the AD brain.

Regarding the progress to date, the research personnel have developed a proximity ligation assay (PLA) to detect alpha-synuclein-alpha-synuclein interactions in human post-mortem brain. Using PLA, no significant alpha-synuclein-alpha-synuclein interactions were detected in AD brain when compared to healthy control human post-mortem brain (Aim 1). PLA to detect alpha-synuclein-tau interactions is currently under development (Aim 2). In addition, Dr. McLean's team has used adeno-associated virus (AAV) to express tau protein in the brains of neonatal mice carrying the human alpha-synuclein transgene to determine the effect of *asyn* overexpression on tau-induced behavior and neuropathology. Mice were injected with tau AAV at birth and are currently aging to the appropriate time point for behavioral analyses and euthanization is examine brain pathology.

The State of Florida has long been a popular choice for retirees looking to live out their golden years in a warm climate. With the baby boomer population reaching retirement age, the aging population in Florida is growing every year. With aging comes the onset of age-related diseases, including dementias such as Alzheimer's disease (AD), Parkinson's disease (PD) and dementia with Lewy Bodies (DLB). Florida is in the unenviable position of having an increasing aging population and by default, an increasing population of patients suffering from dementia, both of which are a formula for a future public health emergency. To date there are no effective treatments, no disease modifying therapeutics, and no cure for dementias such as AD. Decades of research, primarily funded by the NIH, have resulted in the identification of multiple protein targets with the potential for therapeutic development, at the center of which are amyloid-beta and tau. There is a critical, unmet need to identify novel targets for AD therapeutics to treat patients at risk of developing AD or newly diagnosed with AD to halt progression of AD before it is too late.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

6. **Grant #7AZ06:** Impact of Perirhinal Cortical Tau Pathology on Pre-Clinical Cognitive Decline

**Principal Investigator:** Jennifer Bizon, PhD

**Organization:** University of Florida

**Progress Report:** The overarching goal of *Aim 1* is to determine how advanced age influences the aggregation and spread of human wildtype tau delivered to the rat transentorhinal cortex (area 35 of PER), as this brain region develops early tau pathology in humans with Alzheimer's disease. In Dr. Bizon's last report, they summarized the completion of a batch of surgeries that delivered either adeno-associated virus-Tau (AAV-Tau) or control AAV-eGFP to area 35 of PER (n= 30 young and 28 aged). Rats from the 2-month survival period in this cohort have been sacrificed and the research team has begun initial biochemical quantification of tau isoforms and phosphorylation in PER.

Their antibody panel thus far includes the following: anti-tau (raised against peptide corresponding to human tau aa 576-583; recognizes both non- phosphorylated and phosphorylated Ser262; from Abcam; part number ab64193); *cross-reacts with rodent tau*. Secondly, CP27 (raised against peptide corresponding to human tau 130-150; gift from Peter Davies, Dept. of Pathology, Albert Einstein College of Medicine); *does NOT cross-react with rodent tau*. Lastly, 7F2 (raised against synthetic phosphopeptide corresponding to residues 193–211 in 2N/4R human tau with phosphorylated S199, S202 and T205; produced by their collaborator Benoit Giasson, Dept. of Neuroscience, University of Florida); *recognizes AT8 phospho-tau epitope (pSer202-pThr205)*.

For the anti-tau antibody, robust immunoreactivity is observed across all conditions, consistent with the fact that this antibody is known to recognize both native rat and human tau. Notably, however, a band is detected by the anti-tau antibody in the aged AAV-hWtTau rats that is not observed in the other conditions. This band is human tau as it is recognized by CP27 which does not cross-react with rat tau. Moreover, in many aged AAV-hWtTau animals, the same band is detected with a 7F2 antibody which recognizes pSer202-pThr205 (also recognized with AT8 antibody). Together these initial data suggest that human tau delivered to aged rats is becoming hyperphosphorylated in area 35 (the site of delivery) 2 months after AAV delivery. Ongoing experiments will characterize tau in the insoluble fractions from these same animals, will expand this analysis to include additional antibodies recognizing different features of pathological tau, and will expand the cohort to include young and aged rats delivered a mutant version of tau (P301L) at the same 2 month survival time after surgery. Finally, they will process the hippocampus of these same animals to quantify the extent to which tau pathology is occurring in monosynaptic sites outside of the site of AAV-WtTau delivery. Completion of these experiments will be a focus within the next reporting period. Tissue from the other rats is being processed for fluorescence for immunohistochemical analysis of monoclonal antibody (AT8, Alz50) and Thioflavin-S in order to confirm preliminary findings described in previous reports.

The overarching goal of *Aim 2* is to characterize behavioral/cognitive consequences of tau pathology induced by human wildtype tau to the PER of young and aged rats. They

have previously described the refurbishment of some of their specialized behavioral equipment (i.e., olfactometers), which they are beginning to be used for sensitive behavioral assessment of PER function. Additionally, the research team has continued to validate and the test visual stimuli that are morphed to become more similar. They validated two distinct stimulus sets of morphed objects that allow for parametric manipulations of perceptual ambiguity (between 0 and 90% overlap). The team plans to use these images for cognitive testing of the AAV-tau and control rats. Importantly, the ability to use different object pairs will allow for longitudinal assessment as a function of tau aggregation in the PER.

**Follow On Funding:** National Institutes of Health, Total Funds Awarded \$275,000.00

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

7. **Grant #7AZ08:** Pathophysiology of Traumatic Brain Injury in the State of Florida Alzheimer's Disease Initiative Brain Bank

**Principal Investigator:** Dennis W. Dickson, MD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** Specific Aim 1: With discontinued immunohistochemistry reagent kits from Agilent Technologies, Dr. Dickson and associates were able to identify an alternative reagent kit from Biocare Medical. They recently optimized this new kit for use with their CP13 study antibody. Resuming immunohistochemistry staining, they are currently processing the remaining 514 (46% cohort) for completed tau immunohistochemistry.

Specific Aim 2: Complete medical record review has been performed for 840 cases (83% of cohort), and additional record review is ongoing. Data extraction for these 840 cases includes disease course, family history, education, substance use, head trauma, height and weight, and any neurological or neuropsychological testing.

Specific Aim 3: This aim is being performed in collaboration with Dr. Melissa E. Murray (Grant #6AZ01). The researchers have plated 377 cases and controls, which have been shipped to Rochester and are currently undergoing genotyping with the newly named NeuroChip (formerly NeuroX2). An additional 732 DNA samples have been prepared and are currently being organized for plating and shipment to their Medical Genome Facility in Rochester.

**Follow On Funding:** 2017-2018 Younkin Scholars Award (Synaptic Biology Program, at Mayo Clinic).

**Collaborations:** Submitted a multicenter ADRC R01 grant application (Boston University- PI: Ann McKee, Mount Sinai Hospital PI: John Crary, Mayo Clinic- PI: Dennis Dickson) titled "The Contribution of Age-Related Tauopathies to Alzheimer's Disease"

(Role: Co-Investigator).

**Journals:**

Manuscript accepted for publication in the journal Human and Ecological Risk Assessment: Finkel and Bieniek. A Quantitative Risk Assessment for Chronic Traumatic Encephalopathy (CTE) in Football: How Public Health Science Evaluates Evidence.

**Patents:** None at the time of reporting.

8. **Grant #7AZ11:** Antibody Targeting of IL1RAP and Studying their Therapeutic Effects in Mouse Models of Alzheimer's Disease

**Principal Investigator:** Kiminobu Sugaya, PhD

**Organization:** University of Central Florida

**Progress Report:** Alzheimer's disease (AD) is a progressive and devastating disease that causes memory loss and cognitive decline. The pathological feature of AD is gliosis and widespread neuronal loss, which results in a decline of cognitive abilities and an inability to maintain independence and perform normal day to day activities. Through multi-dimensional molecular pathways, amyloid- $\beta$  peptide ( $A\beta$ ) has been determined to be one of the main proteins involved in the plaque formation. Currently, there are no drugs available to control or reverse the progressive symptoms of this disease. Additionally, recent trials of new drugs have failed to yield promising results. A great sense of urgency is existing to investigate new targets and drug carriers in order to overcome AD. Recent discoveries in the gene mechanisms responsible for the clearance of amyloid plaques at early stages of the disease present potential for new drugs development. Specifically, variance in the interleukin-1 receptor accessory protein (IL1RAP) has been associated with an increase in amyloid plaque accumulation. Recent studies have also suggested that targeting IL1RAP may act as a viable approach to increase the clearance of amyloid deposits, providing a mode to control AD. This is because an overexpression of interleukin 1 (IL-1) triggers the activation of microglia to act against  $A\beta$  accumulation, demonstrating an inverse relationship between  $A\beta$  accumulation and microglial activation. Additionally, activation of the IL-1 pathway requires binding of IL1RAP to the IL-1. The *IL1RAP* splice variants induce inhibitory effects on the IL-1 pathway, which indicate the crucial role of the IL1RAP in modulating the pathology of  $A\beta$ . Recent PET imaging studies on Alzheimer's patients by Ramanan et al 2015 clearly demonstrate that the IL1RAP variant had stronger effect on  $A\beta$  accumulation on the progression of the disease than the ApoE e4. New drug developments specifically targeting the IL1RAP immune pathway could enhance the brain's own ability to remove  $A\beta$  in patients carrying the gene variant. Because of this, they propose to develop an antibody-based blocking of IL1RAP activity. Dr. Sugaya and associates propose to use exosomes as antibody delivery vehicles. Exosomes are biological nanoparticles shed from the cells that play an important role in cell-to-cell communication by transfer of mRNA and proteins. Recent studies have demonstrated that exosomes, derived from oligodendrocytes have improved brain integrity. Using exosomes as antibody delivery vehicles will have an added advantage because of their inherent brain protection properties. In addition, exosomes have the potential to cross the blood brain barrier to deliver the target drugs. In this reporting period they developed exosome containing IL1RAP antibodies as a cargo and having brain homing peptide on the surface to targeting delivery to the brain after peripheral injection. To test this

modified therapeutic exosome for neuroprotection, they developed in vitro AD model consist of 3D culture of neural cells derived from AD patient's induced pluripotent stem cells. In order to further enhance antibody delivery into the cells, they will also use nanobodies against IL1RAP. Nanobodies are small recombinant molecules that are antigen-specific and are variable fragments of camelid antibodies.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Vida, M., Bacchus, M., Sugaya\*, K. (2018). Differential sequences of exosomal NANOG DNA as a potential diagnostic cancer marker. PLOS ONE13(5): e0197782.  
<https://doi.org/10.1371/journal.pone.0197782>

Sugaya, K., Vaidya, M. Stem cell therapies for neurodegenerative diseases in: Exosomes, Stem Cells and MicroRNA: Aging, Cancer and Age Related Disorders. ED: Karl L. Mettinger, Pranela Rameshwar, Vinod Kumar Springer, Apr 7, 2018 Volume 1056 of Advances in Experimental Medicine and Biology (ISBN:3319744704, 9783319744704) pp. 61-86

**Patents:** None at the time of reporting.

9. **Grant #7AZ12:** Large-Scale Identification of Genes that Suppress Concurrent Abeta42 and Tau Pathology in Vivo

**Principal Investigator:** Diego E. Rincon-Limas, M.Sc., PhD

**Organization:** University of Florida

**Progress Report:** The main goal of this study is to uncover molecular targets that can modify the concurrent pathology induced by Abeta42+tau. To that end, Dr. Rincon-Limas and associates initiated the first large-scale loss-of-function RNAi screen in flies co-expressing Abeta and tau transgenes in photoreceptor neurons of the Drosophila eye. So far, they have uncovered more than 40 targets that modify pathology in Abeta42+tau flies (see Enhancers and Suppressors sections below). Importantly, some of these modifiers are not previously known to be associated with the onset or progression of Alzheimer's disease (AD) pathogenesis. Thus, this is a highly relevant discovery even when it is at a very preliminary stage. As indicated in previous reports, a number of issues affected the timely progress of the project, particularly during the first two quarters. For instance, due to a significant delay to obtain the required USDA import permit for the introduction of Genetically Engineered Organisms from Europe, this project was activated at the University of Florida until mid-April 2017. Due to this delay, the postdoc that was going to be recruited to work full time on this project decided to go to another institution and thus the PI had to re-initiate the search to recruit another qualified individual. Furthermore, they had additional delays associated with the processing of the material transfer agreement (MTA) between the University of Florida and the Vienna Drosophila Resource Center. UF was not willing to accept some of the initial terms and thus subsequent negotiations to accept and execute the corresponding agreement resulted in a delay to purchase the required collection of Drosophila RNAi lines required to initiate the project on time. Taken together, all these issues contributed

to a major delay in the initiation of the proposed work and, therefore, significant funds remain to be expended. Thus, a 6-month no-cost extension is required to compensate for this significant delay.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

10. **Grant #7AZ13:** CK1 Delta Inhibition to Reduce Sundowning in Alzheimer's Disease

**Principal Investigator:** Danielle Gulick, PhD

**Organization:** University of South Florida

**Progress Report:** Circadian rhythm dysfunctions occur in the majority of patients with Alzheimer's disease. In these patients, they nap frequently during the day and awaken frequently at night, which has negative consequences on their own health and is exhausting for their caregivers. These patients also have sundown syndrome, which means that their symptoms are worst in the late afternoon and evening, and they may have trouble falling asleep at night. Research staff have been studying how a drug, PF-670462 (CK1i), that rescues circadian rhythmicity, improves brain function and patterns of sleep and activity in a model of Alzheimer's disease that corresponds to the early stage of the disease, in order to understand how fixing circadian rhythmicity with drugs or interventions like bright light and exercise may improve outcomes for patients with Alzheimer's disease. So far, research staff have found that circadian dysfunction occurs very early in the disease, and may be associated with a loss of light input from the eyes. Research staff have also found that CK1i decreases the size of pathological amyloid plaques in the brain, one of the key factors in the loss of brain function in Alzheimer's disease. Finally, CK1i drug improves short-term, or working, memory in the same mice, suggesting that the restoration of circadian rhythms may improve cognitive ability. Together, these studies suggest that CK1i or similar therapeutics, like melatonin, are a novel therapeutic route to improve circadian behavior in Alzheimer's disease, and also to slow the progress of the disease and to improve brain function, especially in patients in the early stages of the disease. Future work will also assess lifestyle interventions such as bright light therapy, and the role of changes at the level of the eye, to identify whether vision restoration may actually improve circadian rhythmicity in Alzheimer's disease.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** They have just begun a novel collaboration, working with Dr. Christopher Passaglia in USF's Engineering Department to study electroretinograms in their mice, to understand how retinal degeneration due to amyloid affects vision and circadian rhythmicity.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

11. **Grant #7AZ14:** Precision-Based Assessment for Detection of MCI in Older Adults

**Principal Investigator:** Rosie Curiel, PsyD

**Organization:** University of Miami

**Progress Report:** Dr. Curiel and her team have enrolled fifty-nine participants to date (12/10/2018). They have pre-screened and scheduled nine other older adults that will start their participation in the study before December 31, 2018. During outreach activities recently conducted the team collected a list of thirty-nine older adults that are interested in participating in the study. They are in the process of contacting them to schedule their initial study visit. Thirty-one participants have completed their study MRI. The study team established a collaboration with Unidad of Miami Beach, a community center that serves a diverse community of older adults to provide study activities. This community center is allowing the study team to conduct outreach activities in their facilities to screen, recruit and enroll study participants. This community center is also providing space to conduct the study testing sessions. The team also established a collaboration with Senior Lift Center, the Urban League of Broward and Broward Health to conduct outreach and recruit potential participants.

**Follow On Funding:** National Institute of Health/ National Institute on Aging  
Total Funds Awarded: \$3,032,641.00

**Collaborations:** Doctoral-level students from Nova Southeastern University and Albizu University are completing a clinical research practicum at this project site and are involved with the study as psychometrists. They are also encouraged to work with the PI to analyze the study data to present scientific findings at scientific meetings. Institutional collaborations are strong to carry out the study aims with the Departments of Radiology, Neurology, and Computer Sciences.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

12. **Grant #7AZ17:** Florida Consortium for African-American Alzheimer's Disease Studies (FCA3DS)

**Principal Investigator:** Nilufer Ertekin-Taner, MD, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** Specific Aim 1 Identification of novel AD risk/protective variants: A total of 125 DNA samples from 56 African-American AD cases and 69 African-American non-demented elderly participants have been selected for whole exome sequencing (WES) on an Illumina's HiSeq4000 instrument. This cohort does not overlap with the 250 African-American AD cases and controls for which Dr. Ertekin-Taner and team have already generated WES data as part of the FCA3DS consortium, funded by their Florida Heath Ed and Ethel Moore Alzheimer Research 2015 Consortium grant. Further, these participants have existing plasma samples in which to pursue cell-free RNA based transcriptome and protein measurements. Hence, they are increasing their WES sample

size by 50%. They will also be able to perform associations with plasma transcript and protein levels in the participants who have both WES and plasma RNA/protein measurements, given their study design. Results from the existing WES data were previously published (N'Songo et al., *Neurol Genet.*, 2017, and N'Songo et al., *J Alzheimers Dis.* 2017). Increasing the sample size of their WES cohort will likely enable the identification of additional AD-relevant variants in this unrepresented population. All identified variants that pass WES quality control will be tested for association with AD risk/protection, both at the single variant level and at the gene level, in a joint analysis with the original cohort of 250 cases and controls. Targeted sequencing across 10 candidate AD risk genomic regions for an overlapping set of 380 African-American AD cases and controls was generated as part of a separate Florida Heath Ed and Ethel Moore Alzheimer Research grant (7AZ07) and will also be integrated with the WES data to enable the analysis of haplotypes encompassing both the exonic regions as well as the regulatory non-coding regions of these genes.

Specific Aim 2 Evaluation of cell-free plasma transcripts as AD biomarkers: RNA extraction from plasma is underway for 115 African-American AD cases and 135 African-American non-demented elderly controls. These samples are selected from those individuals whose plasma protein levels are also being measured with the Simoa assays. Plasma transcript counts will be measured using a custom NanoString® panel.

A pilot experiment for the measurement of plasma RNA levels using NanoString® technology was also conducted. Transcript levels in 10 plasma samples were measured using a pre-developed NanoString “CodeSet” that contains probes to measure the expression level of 760 genes previously reported to be implicated in neurodegenerative diseases, including 134 genes involved in neuroinflammation, 41 in lipid metabolism and 78 in angiogenesis. A subset of the 760 gene transcripts that can be measured with this neuropathology panel have been included within the 50-gene custom NanoString® panel that has been designed to measure the plasma transcript levels of genes relevant to AD, including AD genome-wide association study candidate genes and genes implicated in innate immunity.

Gene expression measurements for the 50 genes in the custom NanoString® panel will be completed in house using the NanoString nCounter system. Plasma transcript levels will be analyzed for differential expression, as well as tested for their correlation with genetic variants identified via WES and targeted sequencing.

Specific Aim 3 Evaluation of plasma proteins levels as AD biomarkers: Plasma from 115 African-American AD cases and 135 African-American non-demented elderly controls has been selected to measure plasma protein levels, in house, using a Simoa HD-1 Analyzer. These are the same 250 participants in whose plasma they will also measure cell-free transcriptome levels as described above. The researchers have prioritized the measurement of 5 secreted proteins that are involved in AD and for which predesigned and validated Simoa assays are available. Simoa assays enable detection of protein levels at a wider dynamic range than standard ELISA assays. In addition, Simoa assays are run on the Quanterix Simoa HD-1 Analyzer, which is a fully automated instrument, thus improving precision by reducing experimental variation compared to ELISA assays. Simoa kits for protein quantification will be purchased from Quanterix™ for the measurement of the plasma levels of Aβ42, tau and three cytokines (IL-6, IL-10, TNFα). Plasma protein levels will be analyzed for differential expression, as well as

tested for their correlation with genetic variants identified via WES and targeted sequencing.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** In this grant their two collaborating institutions are University of Florida (Dr. Meredith Wicklund is site PI) and Mount Sinai Miami Medical Center (Dr. Maria Greig-Custo is site PI). They have established a collaboration with Dr. Todd Golde at the University of Florida for the samples that they are collecting under their ADRC. Given that their patient population is predominantly Hispanic, this will provide an outstanding opportunity to determine role of AD risk variants in this minority population that is likewise under-represented in research. They have already genotyped these Hispanic participants for *APOE* genotypes and this data was used in a manuscript under review (Duara et al., submitted). They have also launched a collaboration with Dr. Margaret Pericak-Vance at the University of Miami. The researchers provided her team with the results of an *ABCA7* deletion variant in our African-American WES cohort. Dr. Pericak-Vance's team completed genotyping some of the top genetic variants from our existing African American WES cohort in their independent African-American series where we are now analyzing jointly with our cohort. Further, they have now received the Alzheimer's Disease Genetics Consortium African-American GWAS data, which they are now analyzing to seek additional replication for the top variants in our existing African-American WES cohort.

**Journals:**

Ertekin-Taner, N., Jim, G.R., Chung, J., Mez, J., et al. Transethnic genome-wide scan identifies novel Alzheimer's disease loci. *Alzheimer's Dement.* 2017 Jul;13(7):727-738. doi: 10.1016/j.jalz.2016.12.012. Epub 2017 Feb 7. PMID: 28183528

**Patents:** None at the time of reporting.

13. **Grant #7AZ18:** Brain Amyloid Load and Novel Cognitive Measures in Diverse Ethnic Groups

**Principal Investigator:** David Loewenstein, PhD

**Organization:** University of Miami School of Medicine

**Progress Report:** Dr. Loewenstein's work on examining amyloid positron emission tomography (PET) scans in ethnically diverse populations has been very successful. Results from the Project were reported in June 2018 at the Florida Alzheimer's disease summit and in Grand Rounds for Weil Cornell University, the University of Miami Miller School of Medicine and Florida State University. This investigation has significant impact for Florida since it is the first to focus on failure to recover from proactive semantic interference on a novel cognitive stress test (LASSI-L) and amyloid load and MRIs of Hispanic and African- American individuals at risk for Alzheimer's disease (AD). This is important in that there is a large growing ethnically diverse population in Florida and this study has shown that the LASSI-L is sensitive to early biological changes in the brain related to AD which can provide tools for early detection and treatment as more novel therapies become available.

This focus on the relationship between semantic interference, amyloid load and MRI findings represents a unique opportunity to contribute valuable knowledge to older adults which have been previously underserved in research. To date, the research team has submitted a five-year R01 grant to the National Institutes of Health that carry on this work and the pilot data generated will also be invaluable in an upcoming Florida Alzheimer's Disease consortium grant with the University of Florida, the University of Miami and Mount Sinai Medical Center. They are currently preparing manuscripts regarding their results for publication purposes.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** Florida International University- Malek Adouadi, PhD CATE Center- Neuroimaging Processing of Amyloid PET Scans.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

#### 14. **Grant #7AZ19:** Functionalized Intrabodies as Potential Anti-Tau Therapy

**Principal Investigator:** Yona Levites, PhD

**Organization:** University of Florida

**Progress Report:** The microtubule-associated protein tau (MAPT) plays an important role in multiple neurologic disorders including Alzheimer's disease (AD), frontal temporal dementia (FTDP-17), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). No disease modifying therapy targeting these disorders has proven effective in humans. Recently, anti-tau immunotherapies have emerged as promising therapeutic approaches with several reaching early stage human testing; yet, there is little consensus regarding the properties of an optimal tau-targeting immunotherapy. Building off extensive preliminary data showing that Adeno-associated virus mediated delivery of recombinant antibodies, can reduce tau pathology and modestly slow the progression of tau-induced neurodegeneration, Dr. Levites and her team are testing disease-modifying potential of newly generated anti-tau a single-chain variable fragment (scFvs)/intrabodies and assessing whether they can improve efficacy by using combinations of effective anti-tau intrabodies/scFvs or functionalizing effective anti-tau antibodies/scFvs.

So far, they have established and characterized a novel fast and cost-effective model of tauopathy by delivering AAV expressing mutant tau tagged by a fluorescent protein, to the brains of neonatal mice. They have cloned and demonstrated in vitro target engagement of a number functionalized scFvs and intrabodies, thus expanding on the original proposal and now testing them in vivo. Results of this study will be available in the next 6-8 months. These studies will not only provide a framework for identifying an optimized anti-tau immunotherapy but may provide insight into the mechanism of tau-induced neurodegeneration.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Strang, K. H., Goodwin, M. S., Riffe, C., Moore, B. D., Levites, Y., et al. (2017). Generation and characterization of new monoclonal antibodies targeting the PHF1 and AT8 epitopes on human tau. *Acta Neuropathologica Communications*, 5(1), 58. doi:10.1186/s40478-017-0458-0

**Patents:** Two patents have been filed.

- 1.) UF#16782 Disclosure entitled "New Phospho-Independent tau Antibody 2D1"
- 2.) UF#16620 Disclosure entitled "New Phospho-tau Antibody 7F2"

**15. Grant #7AZ20: The Role of TTC3 in Alzheimer's Disease Pathogenesis**

**Principal Investigator:** Holly N. Cukier, PhD

**Organization:** University of Miami

**Progress Report:** Alzheimer's disease (AD) is the leading cause of dementia and currently affects about 500,000 Floridians. This proposal seeks to further investigate the relationship of AD with the *tetratricopeptide repeat domain 3 (TTC3)* gene. Dr. Cukier's research group recently identified a potentially damaging mutation in the tetratricopeptide repeat domain 3 (*TTC3*) gene in a family of 11 individuals with AD (Cukier, et al, 2016). *TTC3* encodes an E3 ubiquitin ligase protein that plays an important role in AD pathways including protein kinase B (Akt) signaling, negative cell cycle control, and neuronal differentiation. Moreover, these pathways are intertwined with normal neuronal synaptic function, as well as A $\beta$  and tau processing, features of AD pathology. This suggests that *TTC3* could play a protective role against AD; thus, mutations that reduce *TTC3* expression may contribute to AD risk.

The research group has generated three stem cell lines from AD individuals from this family that carry the mutation of interest in *TTC3*. Efforts are ongoing to define the characteristics of neurons generated from these cells as compared to neurons from control individuals to determine what are the cellular features of these cells that may contribute to AD. Their scientists are also attempting genome editing to correct this mutation in these stem cell lines, as well as introducing the mutation into control stem cell lines to determine what cellular features are solely dependent on the *TTC3* mutation. They have successfully generated this *TTC3* mutation in a HEK cell line, which demonstrates that the tools that were designed are appropriate. The next step will be to attempt the editing in stem cell lines. They also have brains from members of this family who carry the *TTC3* mutation. Both brain tissue from these AD patients (old neurons in the late stages of disease) and growing neurons from stem cells of relatives with the *TTC3* mutation (young neurons in the very early stages of disease) will be used to assess expression profiles. Through additional data available from their colleagues, this study will compare the brain and neuronal samples to samples of hundreds of unrelated AD individuals. Through the experiments outlined in this proposal, the research team aims to elucidate the function of *TTC3* and its potential role in cellular mechanisms that drive AD pathogenesis. Furthermore, by utilizing expression data available from additional AD individuals, this study could identify shared and unique pathways of disease and thereby provide a broader understanding of AD pathogenesis.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

16. **Grant #7AZ21:** Evaluating the Mechanism By Which Tau A152t Modulates Risk of Tauopathy

**Principal Investigator:** Casey Cook, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** Pathogenic mutations in the tau gene (MAPT) are linked to the onset of tauopathy, but the A152T variant is unique in acting as a risk factor for a range of disorders including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB). In order to provide insight into the mechanism by which A152T modulates disease risk, a novel mouse model was developed utilizing somatic brain transgenesis with adeno-associated virus (AAV) to drive tau expression *in vivo* and validated the model by confirming the distinct biochemical features of A152T tau in postmortem brain tissue from human carriers. Specifically, TauA152T-AAV mice exhibited increased tau phosphorylation that unlike animals expressing the pathogenic P301L mutation remained localized to the soluble fraction. To investigate the possibility that the A152T variant might alter the phosphorylation state of tau on T152 or the neighboring T153 residue, a novel antibody was generated that revealed significant accumulation of soluble tau species that were hyperphosphorylated on T153 (pT153) in TauA152T-AAV mice, which were absent the soluble fraction of TauP301L- AAV mice. Providing new insight into the role of A152T in modifying risk of tauopathy, as well as validating the TauA152T-AAV model, the results demonstrate that the presence of soluble pT153-positive tau species in human postmortem brain tissue differentiates A152T carriers from noncarriers, independent of disease classification. These findings implicate both phosphorylation of T153 and an altered solubility profile in the mechanism by which A152T modulates disease risk.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

17. **Grant #7AZ22:** ApoE and Cerebrovascular Aging in Alzheimer's Disease

**Principal Investigator:** Takahisa Kanekiyo, MD, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** Brain homeostasis relies on cerebral blood vessels to supply oxygen and nutrients and eliminate carbon dioxide and other toxic metabolites through the

blood-brain barrier (BBB). Thus, impaired cerebral blood flow or BBB breakdown during aging leads to neuronal damage and diffuse white matter lesions, often resulting in vascular cognitive impairment and dementia (VCID). Population-based studies show that VCID and Alzheimer's disease (AD) cause about 70 to 90% of dementia in the aged population. Accumulating evidence has shown that the  $\epsilon 4$  allele of the apolipoprotein E (*ApoE*) gene is a strong genetic risk factor for AD and VCID. ApoE4 not only exacerbates amyloid- $\beta$  ( $A\beta$ ) accumulation in the brain, but also triggers cascades that cause vascular dysfunction, including BBB breakdown and reduction in the number of small vessels. Therefore, Dr. Kanekiyo and associates' overall goal of this project is to determine how cerebrovascular dysregulation during aging contributes to the pathogenic pathways for AD using in vitro and in vivo models. During the reporting period, they have made significant progress toward their goals. In particular, they focused on effects of endothelial senescence on BBB integrity. At the BBB, tight junctions (TJs) between endothelial cells precisely regulate paracellular entry of various molecules from blood flow. TJs are composed of multiple transmembrane proteins, including the junctional adhesion molecules, Occludin and Claudins (Claudin-1, -3 and -5), which connect cytoplasmic regions to actin filaments through Zonula Occludens (ZO-1, -2 and -3). While the actin cytoskeleton interacts with the motor protein myosin II, the phosphorylation of the myosin light chain (MLC) increases contractility of the cytoskeleton, resulting in diminished BBB integrity. Importantly, MLC phosphorylation is strictly regulated by the non-muscle MLC kinase (MLCK), which phosphorylates MLC in a  $Ca^{2+}$ -dependent manner. Thus, they analyzed the MLCK-mediated actin polymerization in endothelial cells. When human endothelial hCMEC/D3 cells were incubated with cobalt chloride ( $CoCl_2$ ) which is a strong reactive oxygen species (ROS) inducer, the actin polymerization and MLCK activity was significantly increased. The pretreatment with an MLCK inhibitor prevented the effect. In addition, they also found that overexpression of p16<sup>INK4a</sup> triggering cellular senescent phenotypes activates MLCK pathway and disturbs the endothelial barrier integrity in both cellular and mouse models. These results suggest that endothelial senescence diminishes BBB integrity during aging, and that controlling the MLCK pathway at the BBB may have beneficial effects on aging-related cognitive impairment. They will continue their study to further assess how vascular aging contributes to the ApoE isoform-dependent mechanisms in following years. There is no major change in the proposed study.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Yamazaki, Y., Kanekiyo, T. (2017). Blood-Brain Barrier Dysfunction and the Pathogenesis of Alzheimer's Disease. *International Journal of Molecular Sciences*. 18. Doi:10.3390/ijms18091965.

**Patents:** None at the time of reporting.

18. **Grant #7AZ23:** System Analysis of Potential Drug Interactions in the Treatment of Alzheimer's Disease from the FDA Reporting System, Electronic Health Records and Protein Interaction Networks

**Principal Investigator:** Feng Cheng, PhD

**Organization:** University of South Florida

**Progress Report:** The relationship between AD drugs and ADE (such as QT-elongation) was also investigated by calculating reporting odds ratio (ROR) and proportional reporting ratio (PRR) values. Dr. Cheng and associates found QT-elongation is significantly associated with Aricept and Namenda. The mechanism is still under investigation.

They continued to retrospectively review patients assessed at an interdisciplinary clinic for dementia assessment. From this they identified patients given cognitive enhancing medications (e.g. cholinesterase inhibitors and NMDA receptor blockers), in which they prospectively reached out to them through sending letters to 180 previous/current patients. Patients, who voluntarily reached back to the research team, they then called and assessed current medication regimen. Through phone calls they also assessed patients' health outcomes such as hospitalizations, falls, comorbidity management (insomnia, depression), and ability to complete daily activities (e.g. feeding and grooming one-self) as well as self-management (e.g. driving to managing own finances). They then compared the data gathered from the USF Health Byrd Alzheimer's Institute to the national database of FAERs through comparison of adverse drug reactions reported in those taking cognitive supporting medication versus those taking cognitive supporting medications (Aricept (donepezil), Razadyne (galantamine), Exelon (rivastigmine), and Namenda (memantine)) and cognitive impairing medications (e.g. benzodiazepines and zolpidem and diphenhydramine).

**Follow On Funding:** None at the time of reporting.

**Collaborations:** Aim 1: Develop a computational model to identify DDIs in Alzheimer's disease (AD) patients from FDA Adverse Event Reporting System (FAERS) records. The relationship between AD drugs and ADE (such as QT-elongation) was also investigated by calculating ROR.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

19. **Grant #7AZ24:** Correction of Tauopathy-Induced Circadian Dysfunction

**Principal Investigator:** Joshua Gamsby, PhD

**Organization:** University of South Florida

**Progress Report:** Sleep cycle disruption is frequently reported by individuals suffering with Alzheimer's disease. Known clinically as a Circadian Rhythm Sleep Disorder (CRSD), this symptom adversely impacts Alzheimer's disease patients and their caregivers, who must provide for them when they are wakeful. The cause of Alzheimer's disease-associated CRSD is most likely due to a perturbation in the circadian clock, which regulates circadian rhythms. Previous findings from Dr. Gamsby's lab, which were supported in part by this award, showed for the first time that tauopathy, a type of pathology associated with neurodegenerative diseases such as Alzheimer's disease, causes a circadian rhythm disruption. Therefore, one of the goals of their original proposal was to investigate the molecular mechanisms underlying how tauopathy

impacts the molecular clock. An additional goal of their original proposal was also to correct the tauopathy-induced circadian rhythm disruption they have previously observed by targeting glycogen synthase 3 beta (GSK3 $\beta$ ) - an enzyme that regulates normal circadian rhythm timing whose function is altered by tauopathy.

Over the past reporting period they have made significant strides towards the aims outlined in their original proposal. Due to space constraints, only the most relevant and impactful findings are highlighted here. First and foremost, they completed and published the preliminary findings presented in their original proposal which demonstrated the disruption of normal circadian rhythm function at both the behavioral and molecular levels in a mouse model of tauopathy, known as the Tg4510 line (cited in section 4 below). This mouse line expresses a mutant form of the tau protein (P301L) in brain regions impacted by Alzheimer's disease. One of the first studies performed after receiving this award was to perform a longitudinal assessment in the Tg4510 line to determine when in the lifespan of this mouse circadian disruption occurs. Interestingly, they observed that the tauopathy-induced circadian disruption occurs as early as 2.5 months of age. Importantly, this suggests that the circadian rhythm disruption is a very early event in the pathogenesis of tauopathy in the Tg4510 line, occurring even prior to neurodegeneration. Another important finding they made is that circadian rhythm disruption occurs in another mouse model of tauopathy, the PS19 line. This mouse line expresses a mutant form of the tau protein (P301S) that differs from the Tg4510 line. The findings in the PS19 line are of importance as it demonstrates that the circadian rhythm disruption they observe in the Tg4510 line isn't simply genetic noise. In circadian rhythm, disruption that will allow them to better address the molecular underpinnings as well as to easily test potential treatments, such as inhibitors to GSK3 $\beta$ . This work is currently ongoing in the lab. Finally, they have uncovered that the phosphorylation of the tau protein itself is potentially circadian regulated. In summary, the work generated thus far from this award have allowed them to make several impactful findings that will enrich the Alzheimer's disease research field.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Stevanovic, K., Yunus, A., Joly-Amado, A., Gordon, M., Gamsby, J., et al. "Disruption of normal circadian clock function in a mouse model of tauopathy." *Exp Neurol.* 2017; 294:58067. Doi:10.1016/j.expneurol.2017.04.025. PubMed PMID:284610004.

**Patents:** None at the time of reporting.

20. **Grant #7AZ25:** Understanding the Molecular Mechanisms of Seeding and Transmission of Wild Type and Mutant Tau

**Principal Investigator:** Benoit Giasson, PhD

**Organization:** University of Florida

**Progress Report:** All of the studies described in the Specific Aims are ongoing or completed. Dr. Giasson and associates have completed most of the studies using HEK293T cells proposed in Aims 1 and these have been published (Strang et al., 2018 J.

Biol. Chem. 293: 2408-2421). Some of the studies using primary cultures have also been submitted for publication (Croft et al under review at Science Translational Medicine). They are also moving forward in finalizing the characterization and analyses with their new monoclonal antibody to tau phosphorylated at phospho-estrogen receptor alpha (Ser305). Most of the somatic brain transgenesis studies (Aim 3) are completed (submitted for publication; Koller et al under review at Neuron) or ongoing. They do not expect any delays or unforeseen issues.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Strang, K. H., Croft, C. L., Sorrentino, Z. A., Chakrabarty, P., Giasson, B. I., et al (2018). Distinct differences in prion-like seeding and aggregation between Tau protein variants provide mechanistic insights into tauopathies. J. Biol. Chem. 293: 2408-2421. doi: 10.1074/jbc.M117.815357.

Croft, C.E., Cruz, P.E., Woody, B.M., Cebalios-Diaz, C., Giasson, B. I., et al. Rapid and robust rAAV-cased brain slice culture models of Alzheimer's and Parkinson's disease inclusion pathologies. Sci Trans Med (under review).

Koller, E.J., De La Cruz, E.G., Machula, T., Ibanez, K.R., Giasson, B.I., et al. Divergent physiological properties of tau variants revealed by somatic brain transgenesis. Neuron (under review)

**Patents:** None at the time of reporting.

21. **Grant #7AZ26:** Preclinical Investigation of an Optimized Formulation of Resveratrol, JOTROL, for Alzheimer's Disease

**Principal Investigator:** Claes Wahlestedt, MD, PhD

**Organization:** University of Miami Miller School of Medicine

**Progress Report:** The purpose of this project is to investigate whether a novel formulation of the natural product resveratrol, named JOTROL, will be efficacious at mitigating Alzheimer's disease-like pathogenesis. During this reporting period, an optimized dose of JOTROL was determined for treatment of animals. Additional mice were purchased, and a cohort of transgenic Alzheimer's disease mouse models (animals engineered to express 3 human genes linked to Alzheimer's) was aged to proceed with the aims. A challenge has been the low quarterly budget for this project, as small batches of mice have to be ordered at a time, and it has not been possible to purchase old mice. Research project staff was thus forced to buy mice young and let them age in their facilities. This does impact the project, but nonetheless research staff has confirmed that JOTROL has increased brain penetrance in mice, and that blood plasma levels are also increased.

Treatment of Alzheimer's mice with JOTROL also revealed that there was a trend to increased recognition memory, although not statistically significant due to low sample size. This is a much-desired effect in Alzheimer's disease where this type of memory is

impaired. More mice will be tested in the future. Another significant set of results during this period was the discovery that JOTROL affects mitochondrial biogenesis as measured by approximately 1.7-fold increased mitochondrial deoxyribonucleic acid (DNA) in JOTROL- treated aged Alzheimer's mice compared to vehicle controls. Indeed, impaired mitochondrial biogenesis has been shown to contribute to mitochondrial dysfunction, a proposed trigger of Alzheimer's disease.

Florida has a fast-growing population of individuals with Alzheimer's disease. If positive results obtained with JOTROL are confirmed, this formulation has the potential to be a highly translational disease-modifying treatment for Alzheimer's patients in Florida and beyond.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** This reporting period, two undergraduate students and two graduate students (pre-doctorate) performed research on this project. They are also constantly collaborating with the Florida-based startup, Jupiter Orphan Therapeutic, as they are the providers of JOTROL.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

## 22. **Grant #7AZ27:** Structure and Toxicity of Amyloid Beta Hetero-Oligomers

**Principal Investigator:** Suren A. Tatulian, PhD

**Organization:** University of Central Florida

**Progress Report:** Aim 1: Identify the effect of AppE on A $\beta$  fibrillogenesis and accompanying structural transitions upon co-aggregation. Structural changes in AP1-42 and the pyroglutamylated ApPE3- $\Delta$ 2 during incubation in an aqueous buffer have been studied by Fourier transform infrared spectroscopy. Aim 2: Determined the critical morphological and atomic-resolution structural distinctions between aggregates formed by AppE alone and combined with unmodified Ap. Solid state NMR studies on Api-42 and ApPE3 $\Delta$ 2 in lipid environment have been continued and data analysis has been conducted.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** Four graduate students (Nabin Kandel, Faisal Abedin, Molla Manjurul Islam, Leslie Davis) and two undergraduate students (Abdel Rahman Naser and Alea Sterling) have been trained/mentored during the reporting period (see below Nabin Kandel has acquired expertise in solid-state NMR spectroscopy by working with Dr. Bo Chen (University of Central Florida Dept, of Physics) and has performed experiments on Api $\Delta$ 2 and AppEM2 peptides embedded in lipid membranes.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

**23. Grant #7AZ28:** Dementia Detection and Treatment Benefits Through Home Health Care as Compared to Clinic Care in a Rural Florida Underserved Population

**Principal Investigator:** Lisa Kirk Wiese, PhD, MSN, RN, PHNA-BC, CNE

**Organization:** Florida Atlantic University

**Progress Report:** Important Findings from Referrals made to Providers following in-home NP assessments. Of the 28 persons referred to providers for follow-assessment, Dr. Wiese and her associates have been able to contact 26 of the patients thus far for self-report: 90% (24) of persons were seen by their provider! They have since determined that most of these visits occurred as a result of a routinely scheduled visit. Only five patients were notified by their provider to come in for a visit. These five patients all saw the same provider. Six of the ten providers have been contacted and have been overwhelmingly positive toward receiving the results of their patients' Motreal Cognitive Assessment (Moca-B) and Quick Dementia Rating Scales. As the Alzheimer's Community Care nurse and as the Lakeside Hospital Community Coordinator indicated, the providers have been receptive to assistance. However, only eight of the 24 (30%) have been started on dementia medications. They are investigating to determine why. The PI will be meeting with each of the providers for qualitative inquiry and will also examine this issue. Cost Savings: Thus far, based on published calculations, there is a potential savings of \$150,000 for the five patients who have received an early diagnosis. This number is expected to grow as they conduct more follow-up and determine if treatment was initiated for the remainder referred for cognitive impairment.

**Impact on the Community from the Screening:** More than the immediate cost-benefit savings from this program is the cost-effectiveness analysis. There is a new awareness in the community of the importance of early dementia detection. A pilot study emerged from these discussions that has important implications for this program of research: Local churches in the area asked that they come to them to conduct cognitive screenings as they have a large number of older adults. This led to an additional site for participants that evolved rapidly, with the assistance of a Haitian Creole Nurse Practitioner who is a church member. The high amount of interest for brain health by these minority older adults has been enlightening. An outcome of this funded pilot study was the need to write a proposal to do faith-based cognitive screenings.

**Church-based Cognitive Screenings:** Offering education in Haitian Creole and using the measures that were translated into Creole as part of the Florida Department of Health funding, they were able to extend screenings to a local minority church community. This added an additional 52 older adults to this work. They are in the process of making referrals to the providers and to the Memory and Wellness Center. They will report on these findings in the next progress report. Of note is that all of these older adults were able to travel to the church, often with assistance, for the program. They are hoping to access members who are home-bound and unable to come to the church.

**Follow On Funding:** None at the time reporting.

**Collaborations:** Dr. Wiese is mentoring a Family Nurse Practitioner who is pursuing her Doctor of Nursing Practice (DNP) at Florida Atlantic University. They collaborated on

adapting this study to a faith-based setting, and it was very successful. This will be reported in more depth in the following quarter, as follow-up provider appointments are just beginning.

**Journals:**

A publication is in press. This was a qualitative inquiry that addressed the target population.

Wiese, L., Williams, C.L., & Galvin, J. (2018; in press). Ethnically diverse rural Florida stakeholder perceptions about cognitive screening. *Aging and Mental Health*.  
<https://doi.org/10.1080/13607863.2018.1525607>.

**Patents:** None at the time of reporting.

**APPENDIX D**  
**FISCAL YEAR 2018-2019 COMPLETED GRANTS**  
(Funding Year 2017-2018)

Grant #	Organization	Principal Investigator	Award Amount	Life To Date Expenditure	Unspent Funds	Executed Date	End Date	Patents	Publications	Follow-on Funding
8AZ09	Mayo Clinic Jacksonville	Melrose, Heather	\$ 99,999	\$ 29,166	\$ 70,833	02/07/2018	06/15/2018	No	No	No
8AZ31	Relinquished							No	No	No

**COMPLETED GRANTS FISCAL YEAR 2018-2019**  
(Funding Year 2017-2018)

1. **Grant #8AZ09:** Targeting Lrrk2 Activity to Modulate Tau Pathology

**Principal Investigator:** Heather Melrose, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** IACUC protocol modifications were submitted to request permission to perform fibril inoculation and ASO surgery and to administer Mli2 orally in chow. Dr. Melrose and her team received 30 C57BL6J mice (20 females and 10 males) from Jackson labs on 3/14/2018. Trio breedings were set up and the first litters began arriving 4/10/2018 and a total of 72 pups were born. The pups received intra-cerebroventricular injection of adeno-associated virus (AAV) WT-tau virus on post-natal day 0. Once the injected mice were 3 months, they were scheduled to receive tau fibrils prepared from human AD brain. In mid-April a personnel change was submitted and approved to remove Ms. DeMeo as a technician and increase Dr. Melrose's effort from 25% to 50%. In May, Dr. Melrose was offered a new position and decided to leave Mayo Clinic. Despite discussions with other investigators at Mayo about the possibility of continuing the project, they felt it was outside their scope and expertise. The decision was made to terminate the project. To minimize animal waste, the 72 injected animals were transferred for use with another for utilization in the tau program. The protocol transfer details were submitted to Florida Department of Health.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

**APPENDIX E**  
**FISCAL YEAR 2018-2019 COMPLETED GRANTS**  
(Funding Year 2016-2017)

Grant #	Organization	Principal Investigator	Award Amount	Life To Date Expenditure	Unspent Funds	Executed Date	End Date	Patents	Publications	Follow-on Funding
7AZ07	Mayo Clinic Jacksonville	Carrasquillo, Minerva	\$ 250,000	\$ 248,652	\$ 1,348	02/01/2017	3/31/2018	No	No	No
7AZ09	University of Miami	Harvey, Philip	\$ 86,792	\$ 83,084	\$ 3,708	2/27/2017	3/31/2018	No	Yes	Yes
7AZ10	University of Florida	Janus, Christopher	\$ 100,000	\$ 100,000	\$ 0	02/14/2017	3/31/2018	No	No	No
7AZ15	Mayo Clinic Jacksonville	Allen, Mariet	\$ 100,000	\$ 99,559	\$ 441	2/06/2017	3/31/2018	No	No	No
7AZ16	Relinquished						3/03/2017			

**COMPLETED GRANTS FISCAL YEAR 2018-2019**  
(Funding Year 2016-2017)

1. **Grant #7AZ07:** Early Detection Biomarkers of Alzheimer's Disease Inflammation and Vascular Risk Factors in African Americans

**Principal Investigator:** Minerva Carrasquillo, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** The overarching goal of the studies being conducted as part of this award is to identify minimally invasive biomarkers for Alzheimer's disease (AD) in African Americans by correlating relevant genetic variation, gene expression and protein changes assessed in blood. To this end Dr. Carrasquillo and her team performed the following experiments a total of 380 African American AD patients and non-demented elderly participants were systematically screened for genetic variants across 10 genes that were hypothesized to influence the risk of AD through their roles in inflammation and cardiovascular risk; a custom gene expression panel was designed to evaluate the expression of 50 genes whose expression has been previously detected in plasma and whose levels may be relevant to AD risk based on these gene's known functions, and these arrays are being utilized to test expression levels in plasma from 192 African American participants; and a subset of these plasma samples are also being tested for the levels of five key inflammation markers in addition to amyloid beta 42 and tau protein.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

2. **Grant #7AZ09:** Post-doctoral Research Fellowship

**Principal Investigator:** Philip Harvey, PhD

**Organization:** University of Miami

**Progress Report:** Dr. Pina trained in geriatric clinical research methodology with Drs. Harvey and secondary mentors, Drs. Loewenstein and Curiel at the University of Miami Center on Aging. She has co-authored several manuscripts that have been accepted for publication in peer-reviewed journals and several abstracts scientific conferences. Dr. Pina integrated well and spent a significant portion of time at the Center on Aging assisting Drs. Harvey, Curiel and Loewenstein on their state and federally funded research projects that focus on cognition and aging, and neuroimaging. Dr. Pina assisted with clinical evaluation of research participants and gained knowledge of how to administer, score and interpret a standardized clinical research battery that is focused on geriatric neuropsychological assessment. She was also exposed to innovative measures and ways to measure memory and cognition in older adults with suspected brain compromise. Dr. Pina participated in diagnostic consensus meetings and received

weekly supervision related to her work on these projects. She also provided supervision to predoctoral practicum students that are training in geriatric neuropsychology. Dr. Pina helped to maintain the operations of the studies and assisted with participant recruitment and retention, collaborated closely with other department such as radiology and nuclear medicine to carry out the proposed work. She also assisted with data management, data integrity and the SPSS database.

**Follow On Funding:** Ed and Ethel Moore AD Research Program. Principle Investigator: Rosie E. Curiel Cid, PsyD. Proposal Submission Date: 8/2017. Grant Executed, 2/19/18. Total Funds Awarded \$89,304.00

**Collaborations:** None at the time of reporting.

**Journals:**

Curiel, R.E., Crocco, E.A., Raffo, A., Guinjoan, S.M., Harvey, P., et al. (2017) Failure to Recover from Proactive Semantic Interference Differentiates Amnesic Mild Cognitive Impairment and PreMCI from Normal Aging after Adjusting for Initial Learning Ability.

Curiel, R.E., Loewenstein, D.A., Rosselli, M., Pirta, D., Harvey, P., et al. (2017). Cross-Cultural Applicability of a Cognitive Stress Test for Preclinical Alzheimer's Disease G.1.

**Patents:** None at the time of reporting.

3. **Grant #7AZ10:** Corticotropin-releasing Hormone (CRH) Immunotherapy for Alzheimer's Disease

**Principal Investigator:** Christopher Janus, PhD

**Organization:** University of Florida

**Progress Report:** Epidemiological data indicates that chronic stress, depression or post-traumatic stress disorder are risk factors for development of Alzheimer's disease (AD). Further, AD patients with comorbid depression manifest more pronounced brain pathology than patients without depression. Finally, it is well established that many, if not most, individuals with AD are under increased stress at various points in their illness. The physiological response to stress is coordinated by the release of corticotropin-releasing hormone (CRH), which regulates the hypothalamic-pituitary-adrenal (HPA) axis. Long-term dysregulation of the HPA leading to increased CRH and cortisol levels has been postulated to underlie abnormal behavior in many neuropsychiatric disorders including AD. Increased levels of plasma cortisol in these diseases correlate with hippocampal atrophy, cognitive deficits and AD dementia. These clinical observations suggest that lowering CRH signaling might improve behavioral symptoms in a number of neuropsychiatric conditions. Notably, CRH and especially its high affinity receptor corticotropin releasing hormone receptor 1 (CRHR1) are expressed rather widely throughout the brain, not just in the hypothalamus or pituitary; thus, action of this hormone can have a widespread effect.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** The research team is collaborating with two labs at the University of Florida. The first is Dr. Eric Krause's lab, which focuses on biochemical aspects of stress. The second lab is Dr. Jennifer Bizon's lab with focuses on cognitive tests.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

4. **Grant #7AZ15:** Identification of Functional Regulatory Variants at Alzheimer's Disease Loci.

**Principal Investigator:** Marriet Allen-Younkin, MD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** The goal of this study is to identify functional regulatory variants at three Alzheimer's disease (AD) risk loci that were previously identified by disease genome-wide association studies (GWAS), and where gene expression regulation has been implicated as the likely disease mechanism. This was to be accomplished through targeted sequencing of deoxyribonucleic acid (DNA) from AD and non-AD subjects, across the three genetic loci. Sequencing was to include both coding and non-coding regions; to ensure capture of all variants that may be linked to the index variants previously identified, the locus was to be defined by linkage disequilibrium. This study is one of two concurrent targeted sequencing projects led by the Principal Investigator. Both of these projects utilize the Agilent HaloplexHS technology, and required development of a custom alignment pipeline for analysis of the sequencing data, working in collaboration with their colleagues in the Mayo Clinic Bioinformatics core. These studies have also enabled further development of quality control operating procedures for targeted sequencing data that will be valuable for these and future projects. This study was introduced as part of a poster presentation at the American Society of Human Genetics annual meeting in Orlando FL (Oct 19, 2017, poster #2000 "Mapping functional regulatory variants at Alzheimer's disease risk loci.") and additional results were presented as a poster at the Alzheimer's Association International Conference (AAIC) in July 2018, held in Chicago (P3-129 Mapping Functional Regulatory Variants at Alzheimer's Disease Risk Loci). There were no changes in scientific programs, shared resources and/or institutional commitments that have impacted the research.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

**APPENDIX F**  
**FISCAL YEAR 2018-2019 COMPLETED GRANTS**  
(Funding Year 2015-2016)

Grant #	Organization	Principal Investigator	Award Amount	Life To Date Expenditure	Unspent Funds	Executed Date	End Date	Patents	Publications	Follow-on Funding
6AZ01	Mayo Clinic Jacksonville	Murray, Melissa	\$ 250,000	\$ 246,226	\$ 3,774	1/29/2016	1/31/2018	No	Yes	Yes
6AZ02	Florida Atlantic University	Galvin, James	\$ 250,000	\$ 230,357	\$ 19,643	2/11/2016	1/31/2018	No	No	Yes
6AZ03	University of Miami	Loewenstein, David	\$ 88,470	\$ 82,151	\$ 6,319	1/28/2016	1/31/2018	No	Yes	No
6AZ04	University of Miami	Czaja, Sara	\$ 249,096	\$ 231,303	\$ 17,793	1/20/2016	1/31/2018	No	No	Yes
6AZ05	University of Florida	Cottler, Linda	\$ 250,000	\$ 232,143	\$ 17,857	2/23/2016	1/31/2018	No	Yes	Yes
6AZ06	Mayo Clinic Jacksonville	Fryer, John	\$ 250,000	\$ 241,283	\$ 8,717	1/29/2016	1/31/2018	No	Yes	No
6AZ07	University of Florida	Wicklund, Meredith	\$ 250,000	\$ 232,143	\$ 17,857	2/23/2016	1/31/2018	No	No	No
6AZ08	University of Miami	Wahlestedt, Claes	\$ 250,000	\$ 249,824	\$ 176	1/20/2016	1/31/2018	No	Yes	No
6AZ09	Florida State University	Terracciano, Antonio	\$ 250,000	\$ 247,983	\$ 2,017	2/11/2016	1/31/2018	No	No	No
6AZ10	University of Florida	Horgas, Ann	\$ 249,436	\$ 231,619	\$ 17,817	2/23/2016	1/31/2018	No	No	No
6AZ11	Florida State University	Meckes, David	\$ 81,499	\$ 81,499	\$ 0	1/29/2016	1/31/2018	No	Yes	No
6AZ12	Mayo Clinic Jacksonville	Lucas, John	\$ 200,000	\$ 185,714	\$ 14,286	2/11/2016	1/31/2018	No	No	Yes
6AZ13	Mayo Clinic Jacksonville	Kim, Jungsu	\$ 200,000	\$ 200,000	\$ 0	1/29/2016	1/31/2018	No	No	No

6AZ14	University of West Florida	Guttman, Rodney	\$ 81,499	\$ 81,386	\$ 113	1/19/2016	1/31/2018	No	No	No
6AZ15	University of Florida	Bowers, Dawn	\$ 100,000	\$ 96,657	\$ 3,343	2/11/2016	1/31/2018	No	No	Yes

**COMPLETED GRANTS FISCAL YEAR 2017-2018**  
(Funding Year 2015-2016)

1. **Grant #6AZ01:** Clinicopathologic and Genetic Differences of Neurodegenerative Health Disparities in the State of Florida Brain Bank

**Principal Investigator:** Melissa E. Murray, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** In summary, the Ed and Ethel Moore Alzheimer Research grant has enabled Dr. Murray to create the FLorida Autopsied MultiEthnic (FLAME) cohort. Utilizing their preliminary data and funded effort over the last two years they have successfully gathered important demographic, clinical, and neuropathologic information. They have utilized the FLAME cohort to write two publications centered on Alzheimer's disease from the perspective of ethnracial differences and sex differences. They had hoped to complement these studies with genetic data, but their dependence on stored deoxyribonucleic acid (DNA) resulted in a delay of data gathering owing to poor quality of many DNA specimens. This work will continue to be pursued by re-extracting fresh DNA for the purpose of performing NeuroChip genotyping to rapidly screen neurodegeneration-associated variants.

**Follow On Funding:** Grant Mechanism: Ed and Ethel Moore Alzheimer's Disease Research Program. Principal Investigator: Melissa E. Murray. Proposal Submission Date: 10/10/2017 Grant Start – End Date: 2/1/2018 to 1/31/2020, Total Funds Requested \$250,000, Total Funds Awarded \$221,000.00

**Collaborations:** None at the time of reporting.

**Journals:**

Shinohara M., Murray M.E., Frank R.D., Shinohara M., et al. (2016) *Impact of sex and ApoE4 on cerebral amyloid angiopathy in Alzheimer's disease*. Acta Neuropathologica 132(2):225-34. PMID: 27179972

Graff-Radford J., Lesnick T.G., Boeve B.F., Przybelski S.A., Murray M.E., et al. (2016) *Predicting survival in Dementia with Lewy Bodies with hippocampal volumetry*. Movement Disorders 31(7):989-94. PMID: 27214825

Lowe V., Curran G., Fang P., Liesinger A.M., Murray M.E., et al. (2016) *An autoradiographic evaluation of AV-1451 Tau PET in dementia*. Acta Neuropathologica Communications 4(1):58. PMID: 27296779

Tacik P., Contreras M.S., DeTure M., Murray M.E., et al. (2016) *Clinicopathologic heterogeneity in FTDP-17 due to MAP1p.P301L mutation including a patient with globular glial tauopathy*. Neuropathology and Applied Neurobiology (Epub ahead of print). PMID: 27859539

Raman M.R., Kantarci K., Murray M.E., Jack Jr. C.R., et al. (2016) *Imaging Markers of Cerebrovascular Pathologies: Pathophysiology, Clinical Presentation, and Risk Factors*. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 18(5):5-14.

PMID: 28054023

McKeith I.G., Boeve B.F., Dickson D.W., Halliday G., Murray M.E., et al. (2017) *Diagnosis and management of dementia with Lewy bodies Fourth consensus report of the DLB consortium*. *Neurology* 89(1):88-100. PMID: 28592453

Babulal G.M., Quiroz Y.T., Arezana-Urquijo E., Astell A.J., Murray M.E., et al. (2018) *Perspectives on Ethnic and Racial Disparities in Alzheimer's Disease and Related Dementias: Update and Areas of Immediate Need*. (Submitted)

Santos O.A., Duara R., Lucas J.A., Greig-Custo M.T., Murray M.E., et al. (2018) *Clinicopathologic Study of Alzheimer's Disease from the Florida Autopsied Multi-Ethnic (FLAME) Cohort*. (In preparation)

**Patents:** None at the time of reporting.

2. **Grant #6AZ02:** Caring For You (C4U): A Novel Intervention to Improve Caregiver and Patient Outcomes and Quality of Life

**Principal Investigator:** James Galvin, MD, MPH

**Organization:** Florida Atlantic University

**Progress Report:** During the last quarter, Dr. Galvin continued with the project. The updated curriculum was completed including additional information on nutrition and mindfulness. Recruitment is ongoing but challenging. While there is great interest in the project, the caregivers need to arrange respite for the patients. Their social worker helps with this. They are fortunate to have a donor gift of \$100,000 gift from the Harry T. Mangurian Foundation to continue the project after Florida funding is completed.

**Follow On Funding:** They received a donor gift of \$100,000 gift from the Harry T. Mangurian Foundation to create enduring materials and continue the project after Florida DOH funding is completed. They recently received another \$1,000,000 gift to, provide additional support and expand the scope of their program. This was recently matched by the Albert Trust with a \$600,000 gift to create patient versions of the program.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

3. **Grant #6AZ03:** Post-doctoral Fellowship in Neuropsychology of Pre-Clinical Alzheimer's Disease

**Principal Investigator:** David Loewenstein, PhD

**Organization:** University of Miami

**Progress Report:** Dr. Penate trained in research methodology and statistics which is run by Drs. Loewenstein, Curiel, Crocco and Czaja at the University of Miami. She has authored a couple of accepted abstracts for the National Academy of Neuropsychology and the International Neuropsychology Society (INS). She has reviewed neuroimaging with Drs. Loewenstein and Duara and learning the MRI visual rating system of the hippocampus, entorhinal cortex and perirhinal cortex. Dr. Penate maintained the SPSS database for ongoing projects and helping Dr. Loewenstein to enter data and to assist with quality assurance. She was in charge of maintaining this database and is learning basic and more advanced statistical analysis of the data by Dr. Loewenstein and Curiel.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Crocco, E., Loewenstein, D.A., Curiel, R., Alperin, N., et al. (2017). A Novel Cognitive Assessment Paradigm to Detect *Pre-Mild Cognitive Impairment (PreMCI)* and the Relationship to Biological Markers of Alzheimer's disease. *Journal of Psychiatric Research*. Aug 24,96:33-38. doi: 10.1016/j.jpsychires.2017.08.015. [Epub ahead of print]

Loewenstein, DA, Curiel, RE, DeKosky, S., Roselli, M., et al. (2017). Recovery from proactive semantic interference and MRI volume: A replication and extension study. *Journal of Alzheimer's Disease*.

Loewenstein, DA, Curiel, RE, Wright, C, Sun, X., Alperin, N, et al. (2017). Recovery from Proactive Semantic Interference in MCI and Normal Aging: Relationship to Atrophy in Brain Regions Vulnerable to Alzheimer's disease. *Journal of Alzheimer's Disease*. 56:3 1119-1126.

**Patents:** None at the time of reporting.

4. **Grant #6AZ04:** A Non-Pharmacological Intervention for Patients with Alzheimer's Disease

**Principal Investigator:** Sara J. Czaja, PhD

**Organization:** University of Miami

**Progress Report:** Dr. Czaja and her team did not experience any challenges, delays or issues during this reporting period and have made significant progress on the project. They have identified, acquired and programmed the technology to deliver the program. They obtained the UM IRB approval for the conduct of the study. They are refining and finalizing the program content in English and Spanish for both study conditions; currently pilot testing the program and have begun their recruitment effort in the community. The research team began their outreach effort July 13, 2017 with their Community Advisory Board. They have recently expanded this effort to include a luncheon with the Pastors of the churches affiliated with the African American community. As part of the study, they also created an Organization Planning Tool to serve as memory and an information organizational aid for the care recipient. They also created a library of virtual tours of Perez Art Museum in Miami, Fairchild Tropical Garden, and Miami Frost Science Museum, and Classical Music presentation so they can be shared between the CG &

CR as part of their pleasant events module. They received a grant from the National Institutes of Health (5R01AG054009) to expand this project. It is funded from 09/01/2016 – 04/30/2021. This grant is providing them with additional resources to expand the recruitment of the project to a large sample of White/Caucasian, Hispanic and African American dyads. They presented an overview of the project as part of an invited symposium at the Annual Meeting of the Gerontological Society of America, July 2017, San Francisco. They have no significant changes in study personnel. With their additional funding from the NIH they were able to hire an African American, Doris Caldwell, to help with recruitment and delivery of the program.

The proposed study will develop and test the efficacy and feasibility of a dyadic-based intervention program (DT), delivered through state-of-the art computer tablet technology, that will focus on both the caregiver and the AD patient and combine an evidenced-based caregiver intervention and an evidenced-based cognitive/functional training for the patient. The program will be tailored to the needs of the caregiver and emphasize issues important to caregivers in the earlier stages of caregiving but will also targets issues across the caregiving trajectory to help prepare the caregiver for changes in their role. The cognitive/functional training will be targeted to the needs of the AD patient. They are in the process of pilot testing and refining the content and website interfaces for the intervention and control conditions for both the caregiver and care recipient. They have on-going efforts in the community to disseminate information about the study. The team now has an African American and a Hispanic on their community outreach team to foster their recruitment with these populations. In addition, they have hosted several meetings with community stakeholders who are aiding with recruitment of participants for the study. They will enter the field and begin data collection in November. Currently, there are no preliminary results or findings from the study. As noted, they did present an overview of the study as part of an invited symposium at the Annual Meeting of the Gerontological Society of America, July 2017, San Francisco. They anticipate accomplishing Aim 1 of the project in the upcoming weeks. They are refining and integrating their current caregiver interventions and cognitive/functional training protocols. They conducted a heuristic analysis of the website/interface usability based on current design guidelines and principles for older adults. They are pilot testing the usability of the interface and study materials with representative samples of White Non-Hispanic, Hispanic and African American dyads. They want to ensure usability and readability of study-related information and materials. The translation of measures/intervention materials not currently available in Spanish will be completed by December 1st. They are using the widely accepted forward translation – back translation method.

**Follow On Funding:** Federal Agency: National Institute on Aging. Grant Mechanism: RO1. Principal Investigator: Sara J. Czaja PhD, David Loewenstein, PhD  
Proposal Submission Date 6/23/2016 Grant Start: 9/1/2016  
Funds Requested: \$3,399,631  
Total Funds Received: \$3,262,583

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

5. **Grant #6AZ05:** Linking Older Adults From the Community in Florida to Memory Screening and Related Health Research

**Principal Investigator:** Linda B. Cottler, PhD, MPH

**Organization:** University of Florida

**Progress Report:** Dr. Cottler and team have interviewed and added to the Florida Registry of Older Adults for Research 999 Florida residents, and screened 191 on the Montreal Cognitive Assessment (MoCA). About 10% scored in a range that necessitated a visit to a Florida Memory Disorder Clinic (MDC). The team continues to build both the Registry and the statewide infrastructure to link older adults to memory screening and related health research through procedure development, volunteer recruitment, expanding network partnerships and training for cognitive impairment screening. To build a more robust workforce throughout Florida capable of conducting this research, they have added significantly to their online workforce development. The researchers constructed an online distance training procedure for new Community Health Workers (CHWs) and volunteers allowing their program to reach all parts of the state. A scheduling tracker has been created to track CHWs' and volunteers' outreach in their communities. They conducted MoCA memory screening training for HealthStreet CHWs and volunteers and certified CHWs to perform the MoCA on community members 65 years of age and older. Volunteers and non-UF students obtained approval to interact with and enroll study participants and view protected health information. The Alzheimer's Disease questionnaire included in the health needs assessment received IRB approval and was added to the HealthStreet intake process for community members 50 years of age and older. Resource Guides have been developed and continuously updated for the 17 counties, with a focus on adding more available resources for Spanish-speakers.

**Follow On Funding:** Florida Department of Health – Ed and Ethel Moore Alzheimer Disease Research Program

Total Funds Awarded: \$200,000.00

**Collaborations:** There has been recent interest and discussion with Dr. Glenn Smith, University of Florida's Chair of the Department of Clinical and Health Psychology, regarding a future partnership with the HABIT@Healthy Action to Benefit Independence & Thinking program in Miami. The HABIT@ program is offered to individuals living with mild cognitive impairment. If a HealthStreet health intake is conducted with older adults +50, an Alzheimer's disease questionnaire and Montreal Cognitive Assessment may also be administered, depending on age. Based on the assessment, the Community Health Workers (CHW) will provide health education materials and/or referrals to Florida Memory Disorder Clinics and HABIT Healthy Action to Benefit Independence and Thinking. The utilization of, satisfaction with and barriers to these needed services, as well as participation in health research, are assessed at 60 and 120 days post assessment in the HealthStreet model. CDOJV /e continue to recruit their volunteer workforce in the counties mentioned in the grant through university/college contacts, as well as through interested community members. Through universities/colleges, they recruit student volunteers through internship programs, which require students to gain practical experience in exchange for college course credit. Many are also individuals committed to volunteering their time. They continue to post volunteer openings on online websites, such as All for Good, Idealist, and Volunteer FL. They have two individuals interested in volunteering in Miami-Dade and Clay counties.

**Journals:**

Milani, S.A., Cottler, L.B., Striley, C. W. (2016). Research Participation and Perceptions among Community Members Who Report a History of Dementia. *Alzheimer's & Dementia*. 12. P823. Doi:10.1016/j.jalz.2016.06.1672.

**Patents:** None at the time of reporting.

6. **Grant #6AZ06:** Clusterin Prevention of Alzheimer Disease Pathology

**Principal Investigator:** John Fryer, PhD

**Organization:** Mayo Clinic of Jacksonville

**Progress Report:** Dr. Fryer and associates have continued to make progress on their understanding of clusterin (CLU) in the pathogenesis of Alzheimer's disease. Alzheimer's pathology is characterized by amyloid plaques composed of the amyloid- $\beta$  (A $\beta$ ) peptide and neurofibrillary tangles composed of hyperphosphorylated forms of tau protein. A third (often under recognized) pathology that is present in >85% of Alzheimer's brains is the deposition of A $\beta$  in the walls of cerebral vessels, termed cerebral amyloid angiopathy (CAA), that can result in small microhemorrhages and large, recurrent, and frequently fatal lobar hemorrhages.

In addition to recently publishing this work in PNAS they have focused their attention on further mechanistic insights into CLU in CAA as well as the role of CLU in tau pathology. Because they found that CLU has such a dramatic role in CAA, they performed an RNAseq (RNA sequencing) profiling experiment to try to uncover molecular signatures associated with the development of CAA in mouse models. This has revealed exciting new data of downstream pathways that may be impacted by CAA and exacerbated by CLU.

**Follow on Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Wojtas, A.M., Kang, S.S., Olley B.M., Gatherer M., Fryer, J., et al. "Loss of clusterin shifts amyloid deposition to the cerebrovasculature via disruption of perivascular drainage pathways." *Proc Natl Acad Sci U S A*. 2017 Aug 15;114(33):E6962-E6971. doi: 10.1073/pnas.1701137114. Epub 2017 Jul 12. PMID: 28701379

**Patents:** None at the time of reporting.

7. **Grant #6AZ07:** Consortium for Diagnostic Algorithm with Novel Markers in Early Alzheimer's Disease

**Principal Investigator:** Meredith Wicklund, MD

**Organization:** University of Florida

**Progress Report:** Through previously funded research (Duara et al, 2010), the ability to obtain a consensus diagnosis was determined to be more efficient without compromising integrity when utilizing an algorithmic method; this diagnosis is called diagnostic algorithm (AlgDx). The AlgDX is an algorithm to determine cognitive state of a patient using the physician diagnosis (PhDX) and neuropsychological diagnosis (NPDx). The novelty of the AlgDx is that it helps to avoid individual bias and also saves time among multisite studies of MCI and dementia.

Through this grant mechanism, Dr. Wicklund and associates were able to build a computerized algorithm where the PhDX and NPDx can be extracted through databanks and calculate the AlgDx. In addition, the calculator has been embedded in website for easy use, validation, and implantation among all consortium researchers. The goal is to validate this method, determine its efficiency and broadly disseminate for clinical use, if applicable.

In addition, they have recruited subjects across the cognitive spectrum to undergo novel neuropsychological measures via standardized administration. The data has been combined with subjects recruited at Mount Sinai Medical Center in Miami through the 1Florida ADRC. The goal is to determine if these neuropsychological measures are more sensitive than data indicates that the Object Recognition Discrimination Task (ORDT) elucidates earlier cognitive decline than traditional memory measures, including Logical Memory and Hopkins Verbal Learning Test-Revised (HVLTR). In addition, analysis found that the pre-exposure trials of ORDT impairs performance of Cognitively Normal participants, because familiarity to the non-target object interferes with recognition of the target object. In contrast, pre-exposure improved the performance of the amnesic mild cognitive impairment (aMCI) and Dementia groups, possible because familiarity with the non-target was not strong enough to result in false recognition or interference.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

8. **Grant #6AZ08:** Epigenetic Modulation of Alzheimer's Disease Hallmarks

**Principal Investigator:** Claes Wahlestedt, MD, PhD

**Organization:** University of Miami

**Progress Report:** This project has been a successful venture. Both aims have been completed. The first aim was published in October 2017 in the US Proceedings of National Academy of Sciences. Dr. Wahlestedt and team have demonstrated that the HDAC inhibitor (HDACi) M344 is not cytotoxic compared to other HDACis tested, and that it can prevent Alzheimer's Disease (AD) like molecular and cellular phenotype, normalize genes and improve memory in the triple transgenic mouse model of AD. The

research team demonstrated that pharmacologically inhibiting histone deacetylase 3 (HDAC3) with a small molecule reverses learning and memory impairment in aged triple transgenic AD mice. This small molecule, CTI-350, can also normalize the expression Ad-related genes. This work is being written up in a manuscript that will be submitted for publication.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Volmar, C-H., Salah-Uddin, H., Janczura, K., Halley, P., Wahlestedt, C., et al. (2017). M344 promotes nonamyloidogenic amyloid precursor protein processing while normalizing Alzheimer's disease genes and improving memory. *Proceeding of the National Academy of Sciences (PNAS)*.

**Patents:** None at the time of reporting.

9. **Grant #6AZ09:** Optimization of "Powerful Tools" for Caregivers of Dementia Patients

**Principal Investigator:** Antonio Terracciano, PhD

**Organization:** Florida State University

**Progress Report:** As of this report's date, data analysis is still being conducted; therefore, Dr. Terracciano and associates have no scientific accomplishments to report. Once data analysis is complete, they plan to write manuscripts for submission to peer/reviewed academic Journals and conferences.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

10. **Grant #6AZ10:** An Analgesic Trial to Reduce Pain and Behavior Disruptions in Nursing Home Residents

**Principal Investigator:** Ann L. Horgas, PhD

**Organization:** University of Florida

**Progress Report:** "Behavioral expressions" of dementia (e.g., neuropsychiatric symptoms or "disruptive behaviors") affect up to 90% of persons with dementia. Symptoms include agitation, aggression, depression, and wandering, and are a major source of patient and caregiver distress, nursing home placement, antipsychotic medication use, restraints, and increased health care costs. Dr. Horgas' prior research demonstrated that, among Florida nursing home residents (N=56,577), those with dementia and pain displayed more aggression/agitation than those without pain. In a

pilot study aimed at reducing pain in community-dwelling adults with moderate to severe dementia (N=3; single-subject design), they demonstrated that regular scheduled acetaminophen (1300 mg every 8 hours) reduced behavioral pain expressions of pain (e.g., grimacing, vocalizations) during active treatment and that pain returned to baseline after drug withdrawal. Clinical guidelines recommend acetaminophen as the first line analgesic for treating pain in older adults. The research team sought to extend this prior work by conducting a trial of routine analgesics in a sample of older adults with moderate to severe dementia. The protocol included administration of acetaminophen, 650 mg by mouth, 3 times per day for four weeks [maximum dose = 1,950 mg per 24 hours; below the current Food and Drug Administration (FDA) recommendations of maximum 3,000 mg/day]. The primary aim was to evaluate the effectiveness of acetaminophen in reducing pain intensity (verbal and behavioral indicators of pain) and behavioral expressions (e.g., agitation and aggression) of dementia. They were unable to achieve this aim because they were unable to recruit patients for this study. There were no changes to the study personnel and no significant institutional barriers to conducting this research. Because the study protocol involved administering acetaminophen, the Institutional Review Board (IRB) did require that additional eligibility criteria be applied. Almost 50% of the screened patients were deemed ineligible due to medication or medical contraindications, such as taking warfarin. Until the end of the study award period, they actively recruited for this study. The research team screened medical records, clinic schedules, conducted information sessions, added new recruitment sites, and 5 consulted with recruitment experts. Recruitment remained a significant challenge to this study. Their activities, barriers encountered, and their strategies to address them are described in the following sections. Despite all efforts, they enrolled 4 participants: 1 completed the study, 1 withdrew, 1 was a screen failure, and 1 was lost to follow-up before the intervention began.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

11. **Grant #6AZ11:** Blood Exosomes and Neurodegenerative Disease

**Principal Investigator:** David G. Meckes, Jr., PhD

**Organization:** Florida State University

**Progress Report:** During the current reporting period Dr. Meckes and associates validated potential biomarkers identified by mass spectrometry that are present in brain-derived exosomes from the preclinical mouse models of Alzheimer's disease (AD). Exosomes were purified from brain tissue of healthy and AD brains at 8 and 10 months of age and analyzed by western blot for vascular cell adhesion molecule-1 (VCAM-1), calreticulin, ras-related protein Rab-8A (Rab8a), amyloid precursor protein processing (APP), Stathmin, and known exosomes markers ALIX, tumor susceptibility gene 101 (TSG101), and a lysosomal protein (CD63). Elevated levels of Calreticulin and VCAM-1 were present in AD when compared to exosomes from healthy animals. Additionally, Rab8a was found to be greatly reduced in the AD exosomes. Together, these data

suggest that the levels of Calreticulin, vacuolating cytoxin protein A (VACAM-1), and Rab8a may represent novel biomarkers to distinguish healthy from AD brains. They are now determining the levels of these proteins in exosomes isolated from younger animals to determine whether they are also early predictors of disease. As exosomes can cross the blood-brain barrier and brain-derived exosomes have been found in the blood, the team are currently testing if the levels of these markers are also changed in exosomes isolated from the blood of the animals. For this, methods were developed to purify the exosomes from the blood and have begun the initial analyses. In addition to analyzing these protein markers, the researchers have purified exosomes from the blood for deep sequencing of small ribonucleic acids (RNAs) to look for differences in exosomal RNA content during AD progression in the mouse model. Results obtained and confirmed in the mice will be tested in patient samples. They now have completed cognitive testing and sample collection from thirty patients and have worked out the methods for exosome purification using size exclusion chromatography. They have determined the amount of plasma to obtain enough exosomal proteins and nucleic acids for downstream analyses and will continue the purifications and proceed with the RNA-Sequencing (RNA-Seq) experiments described in the grant.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:**

Hurwitz, S.N., Sun, L., Cole, K.Y., Ford III, C.R., Meckes Jr., D.G., et al. (2018) An optimized method for enrichment of whole brain-derived extracellular vesicles reveals insight into neurodegenerative processes in a mouse model of Alzheimer's disease. *J Neurosci Methods*. 307. 210-220. <https://doi.org/10.1016/j.jneumeth.2018.05.022>.

**Patents:** None at the time of reporting.

12. **Grant #6AZ12:** Neuropsychological Norms for Ethnically Diverse Florida Elders

**Principal Investigator:** John Lucas, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** The goal of this proposal is to collect normative data from a sample of 450 ethnically diverse Florida elders on a brief, standardized neuropsychological test battery. To date, two of the three consortium sites (Mayo Clinic Florida & Mount Sinai Medical Center) have enrolled 386 participants (86% of target sample). Of those currently enrolled, 116 self-identify as African American (non-Hispanic), 110 as Caucasian (non-Hispanic), and 160 Hispanic. The third consortium site University of South Florida (USF) was the final research institution to initiate the study and enroll participants. The prolonged delay at the USF site was due to the site Principal Investigator transitioning to a new Department in 2016. The data sharing agreement between Mayo Clinic Florida and the University of Florida Alzheimer's Disease Research Center was completed and Dr. Lucas and associates have created a merged dataset containing study data from the Mayo Clinic and Mount Sinai Medical Center sites. USF participants will be added to the dataset.

**Follow On Funding:** National Institute on Aging/ Advancing Reliable Measurement in Alzheimer's Disease and cognitive Aging (ARMADA)  
Total Funds Awarded \$2,538,663.00

**Collaborations:** This project is collaborating with Mount Sinai Medical Center and the University of South Florida.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

13. **Grant #6AZ13:** Targeting ApoE for Alzheimer's Disease Drug Discovery

**Principal Investigator:** Jungsu Kim, PhD

**Organization:** Mayo Clinic Jacksonville

**Progress Report:** By far the strongest genetic risk factor for Alzheimer disease is apolipoprotein (ApoE) genotype. There are several mechanisms by which ApoE may influence AD pathogenesis including possible effects of ApoE on brain cholesterol/lipid metabolism, inflammation, synaptic plasticity, and tau. While it is likely that ApoE participates in some of these processes, overwhelming evidence suggests that one of the major ways that ApoE influences AD is via its effects on Ap metabolism and aggregation. Decreasing ApoE levels results in increased soluble Ap clearance from the brain and markedly reduced Ap deposits in the brain. Thus, understanding how ApoE levels are regulated in the brain will provide important insights into AD pathogenesis as well as new potential treatment targets. Dr. Kim and associates identified Inducible Degradable of LDLR (IDOL) protein as a modulator of Low density lipoprotein receptor (LDLR). LDLR is a cell surface ApoE receptor that plays an important role in mediating the removal of cholesterol. The team demonstrated that IDOL may be a good therapeutic target for Alzheimer's disease because the deletion of IDOL gene decreased the levels of ApoE and Ap in the brain. Furthermore, several small compounds that inhibit IDOL function were identified. There has been no major change in the key personnel and scientific program

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

14. **Grant #6AZ14:** Enhancing Detection of Alzheimer's Disease Biomarkers Using Phage-Derived Quantification (Pdq)

**Principal Investigator:** Rodney Guttman, PhD

**Organization:** University of West Florida

**Progress Report:** During the funding period Dr. Guttman and his team accomplished the major goal of proof of principal that phase-display can be used to identify different phosphorylation states of the tau protein that are currently believed to be pathologically relevant and useful in the confirmation of Alzheimer's disease diagnosis. Changes in resources that were beneficial included Institutional support for students to work in the lab as well as a major piece of equipment. These two changes were unanticipated but were helpful in maintaining progress.

**Follow On Funding:** None at the time of reporting.

**Collaborations:** None at the time of reporting.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

15. **Grant #6AZ15:** Pilot Intervention in Mild Cognitive Impairment: A Proof of Concept Study with Near Infrared Stimulation (NIR)

**Principal Investigator:** Dawn Bowers, PhD

**Organization:** University of Florida

**Progress Report:** Based on funding Dr. Bowers received from the Ed and Ethel Moore Alzheimer Research program, she conducted a small double blinded randomized pilot project to learn whether use of near infrared stimulation (NIR) might be a viable intervention for memory and cognitive difficulties experienced by older adults at risk for transitioning to Alzheimer's disease. This was a proof of concept study conducted under the Rapid Pilot project to help them obtain pilot data that would influence decisions to move forward or not. Design-wise, their participants were randomly assigned to NIR intervention or a sham intervention. The presumed mechanism underlying this intervention relates to potential changes in mitochondrial function, leading improvements in overall cellular health.

This proof of concept study provided preliminary evidence that a two-week intervention involving transcranial NIR stimulation with older adults is feasible, safe, and tolerable and may improve delayed spatial memory and learning performance, not due to changes in mood while also improving working memory and verbal fluency. Additionally, this method may decrease self-reported negative affect, depression symptoms, and anxiety; protect against stress and decrease in sense of psychological wellbeing. While also modulating neuronal biomarkers of cellular metabolism based on magnetic resonance spectroscopy (MRS) findings. This is the first study to their knowledge to directly examine in humans the neural correlates of NIR stimulation cellular. Due to a small sample size, the team primarily conducted effect size analyses.

Overall, the findings obtained from this small pilot project are promising and have provided the following; pilot data necessary for new grant applications (Fogarty, McKnight Brain Research Foundation, National Institutes of Health (NIH)/National Institute on Aging (NIA)). One grant has been funded (Fogarty), one is under review (McKnight), and one was submitted in June 2018 (NIH). The development of multi-site collaborations with colleagues in India (National Institute of Mental Health and

Neuroscience (NIMHANS), Bangalore) and the University of Arizona. Additionally the research has led to one review article that is under review. Lastly, this grant has led to training of post-doctoral, graduate and undergraduate students in experimental and conceptual aspects of clinical trial design.

**Follow On Funding:** This grant was awarded to Dr. Preeti Sinha, M.D., a geriatric psychiatrist, from the NIMHANS of Bangalore, India. Dr. Bowers served as a mentor and consultant on this project.

Federal Agency/Institute: National Institute of Health Fogarty (Cottler)

Total Funds Awarded: \$15,000.00

**Collaborations:** Funding by the Ed and Ethel Moore program has led to new collaborations with two different research groups, one in the United States (University of Arizona) and one in Bangalore, India (NIMHANS). The University of Arizona, Dr. Gene Alexander, Professor and Director of Brain Imaging Laboratory). They are involved in two multisite research grant applications with Dr. Gene Alexander's team at the University of Arizona. One grant was submitted in October 2017 to the McKnight Research Foundation. It underwent two levels of review; reviews were favorable, and they are now awaiting final decision by the McKnight Trustees. The second grant is a larger R01 that will be submitted in June 2018. Both grant applications have relied on the pilot behavioral and neuroimaging data obtained from funding via the Ed and Ethel Moore pilot program.

This project is also in collaboration with the National Institute of Mental Health and Neurosciences (NIMHANS) in Bangalore, India (Dr. Preeti Sinha, Associate Professor). They have ongoing multi-cultural research collaboration that includes a pilot grant, funded by the Fogarty Foundation, to examine effects of NIR stimulation on mood and cognition in healthy and psychiatrically disturbance individuals.

**Journals:** None at the time of reporting.

**Patents:** None at the time of reporting.

## REFERENCES

1. Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia* 2018;14(3):367-429).
2. Gurland BJ, Wilder DE, Lantigua R, Stern Y, Chen J, Killeffer EH, et al. Rates of dementia in three ethnorracial groups. *Int J Geriatr Psychiatry* 1999;14(6):481-93.
3. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older latinos: The influence of type 2 diabetes mellitus, stroke and genetic factors. *J Am Geriatr Soc* 2003;51:169-77.
4. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 Census. *Neurology* 2013;80(19):1778-83.
5. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):263-9.
6. National Institute on Aging, National Institutes of Health. Alzheimer's Disease Fact Sheet. 2016; *NIH Publication No.* 16-AG-6423.
7. Potter GG, Plassman BL, Burke JR, Kabeto MU, Langa KM, Llewellyn DJ, et al. Cognitive performance and informant reports in the diagnosis of cognitive impairment and dementia in African Americans and whites. *Alzheimers Dement* 2009;5(6):445-53.
8. Samper-Ternent R, Kuo YF, Ray LA, Ottenbacher KJ, Markides KS, Al Snih S. Prevalence of health conditions and predictors of mortality in oldest old Mexican Americans and non-Hispanic whites. *J Am Med Dir Assn* 2012;13(3):254-9.
9. Section 381.82, Florida Statutes, [http://www.leg.state.fl.us/statutes/index.cfm?mode=View20Statutes&SubMenu=1&Appmode=Display\\_Statute&Search\\_String=381.82&URL=0300-0399/0381/Sections/0381.82.html](http://www.leg.state.fl.us/statutes/index.cfm?mode=View20Statutes&SubMenu=1&Appmode=Display_Statute&Search_String=381.82&URL=0300-0399/0381/Sections/0381.82.html)
10. U.S. Department of Health & Human Services. (2018). *Funding*. Retrieved from National Institutes of Health (NIH): [https://report.nih.gov/categorical\\_spending\\_project\\_listing.aspx?FY=2017&ARRA=N&D Cat=Alzheimer's Disease](https://report.nih.gov/categorical_spending_project_listing.aspx?FY=2017&ARRA=N&D Cat=Alzheimer's Disease)