Alzheimer's Disease Research Grant Advisory Board

Ed and Ethel Moore Alzheimer's Disease Research Program

February 2022 Report

Ron DeSantis
Governor

Joseph A. Ladapo, MD, PhD
State Surgeon General

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

Alzheimer's disease (AD) is a debilitating brain disease that affects an estimated 6.2 million Americans over the age of 65.[1] Florida is the third most populous state in the nation and has the second highest percentage of adults age 65 and older. In 2020, it was estimated that 580,000 Floridians over the age of 65 were living with AD and this number is projected to reach 720,000 by 2025.[2] AD is the eighth leading cause of death in Florida, and the sixth leading cause of death nationally.[1,3] The estimated 580,000 Floridians living with AD does not include those under the age of 65, or those living with other forms of dementia.

The progression of AD or other related dementias (ADRD) should be viewed as a continuum, over a lifetime, that may begin even when the brain shows healthy functioning. Over the course of many years, cognitive changes occur in the brain that can eventually result in mild cognitive impairment. Nearly 90% of Americans say that if they were exhibiting confusion and memory loss, they would want to know if the cause of the symptoms was AD.[4] Yet, over half of people aged 45 and older with subjective cognitive decline have not talked with a healthcare provider about their questions, concerns, and fears.[4] Among those whose memory problems were creating functional difficulties, 42% had not shared these issues with a provider.[4]

Missed diagnoses of dementia are more common among Black Americans than White Americans. While Black Americans are two times more likely to have ADRD than White Americans, they are only 36% more likely to receive a diagnosis.[5] Also, both Black Americans and Hispanic Americans with cognitive impairment are less likely than White Americans to say that a doctor has told them they have a "memory-related disease."[5]

Beyond the impact of the disease on the individual, AD also affects family members who often serve as caregivers. Alzheimer's disease can span up to 20 years and is emotionally, physically, and financially challenging to caregivers. In 2014, there were nearly 1.1 million caregivers for persons with AD in the state of Florida. More than half of these caregivers (54%) provided four to nine years of care, with an additional 17% providing nine or more years of care.[6]

To combat these statistics, the 2014 Florida Legislature created the Ed and Ethel Moore Alzheimer's Disease Research Program (Program) that was signed and enacted by then Governor Rick Scott. Currently, there are 68 active research grants. 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, 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

The Alzheimer's Disease Research Grant Advisory Board (Advisory Board) is authorized in section 381.82, Florida Statutes, and 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 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.[7]

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 15, 2021, are listed below (Biographical Statements or Curriculum Vitae are available upon request):

Gerontologists:
Leilani Doty, PhD, Chair
Retired, Director of the University of Florida Cognitive and Memory Disorder Clinic

The second Gerontologist position is currently vacant.

Geriatric Psychiatrists:
Josepha A. Cheong, MD
Professor of Psychiatry and Neurology, University of Florida
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:
Neill Graff-Radford, MD
Professor of Neurology, Department of Neurology
Mayo Clinic Jacksonville

James Galvin, MD, MPH
Professor
University of Miami Miller School of Medicine

Ruth Henchey, MD
General Neurology
Baptist Hospital and West Florida Hospital

NATIONAL INSTITUTES OF HEALTH (NIH) STATE RANKING IN TOTAL AMOUNT OF ALZHEIMER'S DISEASE RESEARCH FUNDING

Since the inception of the Ed and Ethel Moore Alzheimer's Disease Research Program in 2014, Florida continues to increase in federal funding that supports Florida researchers. Florida is currently positioned in the top 10 for federal follow-on funding (Figure 1).[8] Florida is one of two states 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 fifth highest growth in new research funding, behind the states of Wisconsin, Ohio, Michigan, and Georgia (Figures 2 and 3).[8]

Figure 1: NIH Alzheimer's Disease Research
State Funding and Rankings for Federal Fiscal Year 2020

State	Total Funding	Rank
California	$444,925,684.00	1
New York	$293,736,104.00	2
Massachusetts	$243,207,492.00	3
Pennsylvania	$199,693,290.00	4
Maryland	$131,335,712.00	5
Texas	$113,837,290.00	6
Missouri	$105,420,677.00	7
Illinois	$103,403,166.00	8
North Carolina	$92,078,733.00	9
Florida	$84,357,177.00	10
Minnesota	$65,622,984.00	11
Indiana	$65,520,691.00	12
Washington	$62,681,242.00	13
Ohio	$58,274,024.00	14
Michigan	$53,842,541.00	15
Arizona	$41,186,151.00	16
Georgia	$38,859,617.00	17
Tennessee	$38,834,164.00	18
Rhode Island	$37,989,310.00	19
Connecticut	$34,833,730.00	20

Fig.1 NIH Research Funding from the 2020 Fiscal Year Reporting Period: The top twenty ranked states in NIH funding for Alzheimer's disease are displayed. With over $84.3 million in NIH funding, Florida is ranked tenth in the nation. *Source: National Center for Health Statistics, National Institutes of Health 2020.*

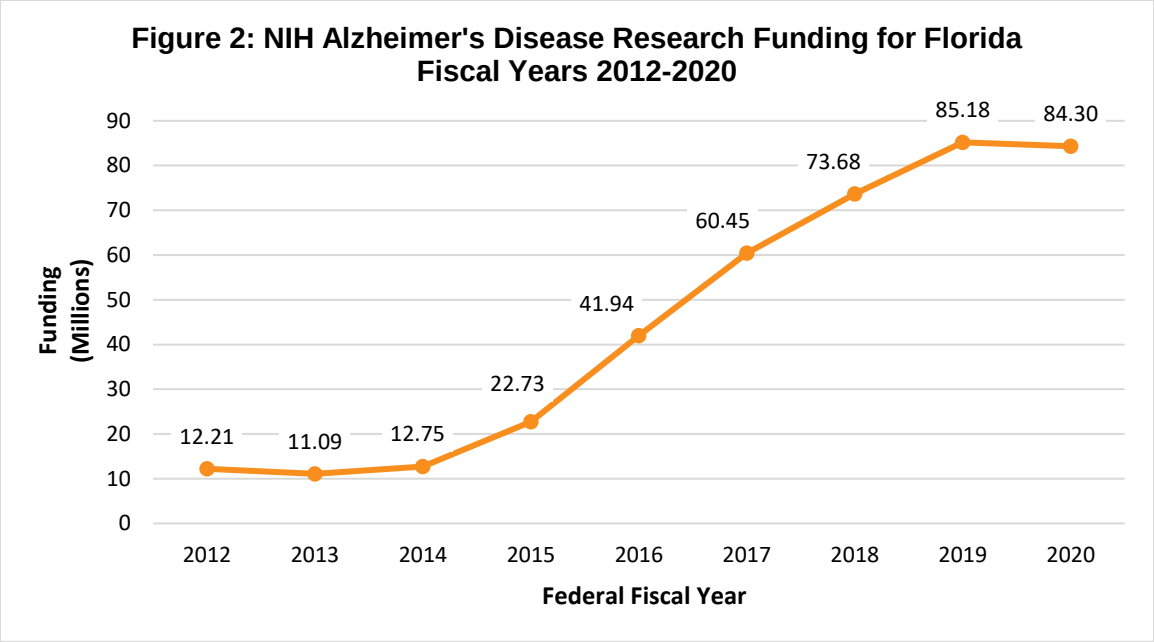

Fig. 2 NIH Research Funding Trends in Florida Fiscal Year 2012-2020: This chart illustrates the recent trends in federal funding for Alzheimer's disease research in the state of Florida. Following three years of relative stability in funding levels, fiscal years 2015-2018 saw a vast increase of funding leading to a 503 percent increase of funding since 2014. In fiscal year 2019, Florida's total federal funding increased by $11.5 million. *Source: National Center for Health Statistics, National Institutes of Health 2020.*

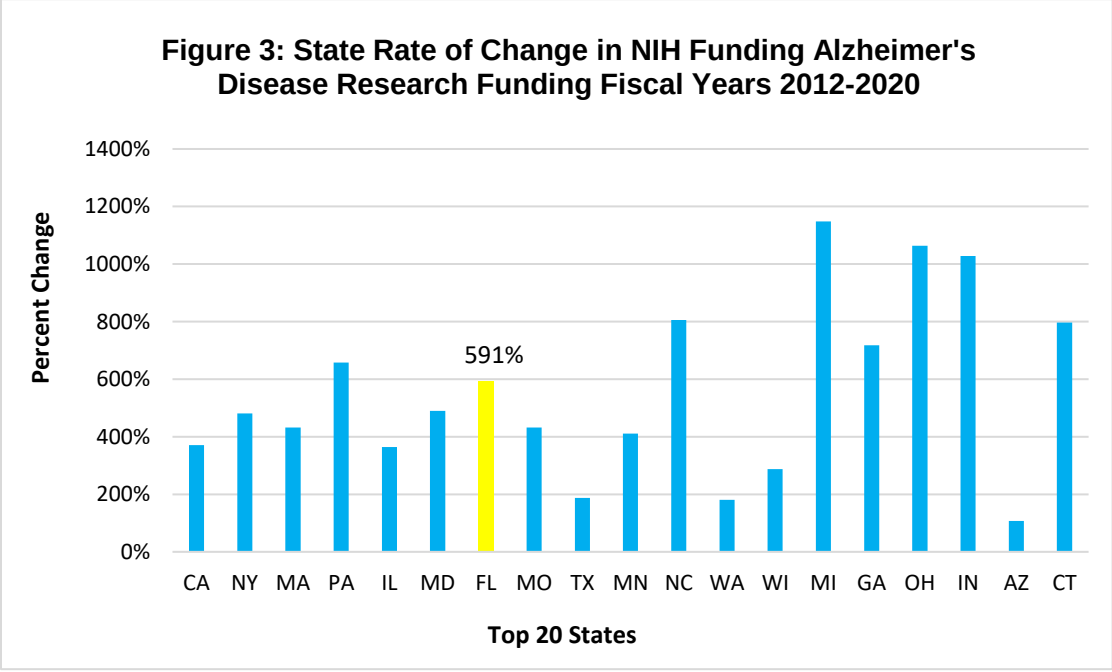

Fig. 3 Change in NIH Research Funding in the Top 20 States Fiscal Years 2012-2020: This graph displays the rate of change in federal Alzheimer's disease research funding for the Top 20 states for fiscal years 2012-2020. Among the Top 10 ranked states in NIH funding for Alzheimer's disease, Florida saw the third highest funding gains since 2012 (591%). *Source: National Center for Health Statistics, National Institutes of Health 2020.*

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 and are listed below:

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

In state fiscal year 2021-2022, the legislature provided $5 million for research grants. Appendix A details all newly awarded grants and Appendix B details all active grants in 2020-2021. Information on research progress, follow-on funding, publications, and patents for each active grant is included in Appendix B.

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 among 17 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 the 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.

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

APPENDIX A
Fiscal Year 2021-2022 Newly Awarded Grants (Announced December 15, 2021)
(Funding Year 2021-2022)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
22A01	Florida Atlantic University	Randy Blakely, PhD	$ 349,819	3/31/2024	No	No	No
22A02	Florida Atlantic University	Lisa Wiese, PhD, MSN, RN, GERO-BC, PHNA-BC, CNE	$ 250,000	3/31/2026	No	No	No
22A03	Florida State University	Robert Tomko Jr., PhD	$ 100,000	3/31/2024	No	No	No
22A04	Mayo Clinic	Yang You, PhD	$ 100,000	4/01/2024	No	No	No
22A05	Mayo Clinic	Shunsuke Koga, MD	$ 100,000	4/02/2024	No	No	No
22A06	Mayo Clinic	Mariet Allen, PhD	$ 100,000	3/31/2023	No	No	No
22A07	Mayo Clinic	Fabienne Fiesel, PhD	$ 350,000	3/31/2026	No	No	No
22A08	Mayo Clinic	Yasuteru Inoue. MD, PhD	$ 100,000	3/31/2024	No	No	No
22A09	Mayo Clinic	Nilufer Ertekin-Taner MD, PhD	$ 350,000	3/31/2024	No	No	No
22A10	University of Central Florida	Nichole Lighthall, PhD	$ 742,833	3/31/2026	No	No	No
22A11	University of Florida	Jeremy Grant, PhD	$ 99,569	3/31/2024	No	No	No
22A12	University of Florida	Adam Barnas, PhD	$ 100,000	3/31/2024	No	No	No
22A13	University of Florida	Jada Lewis, PhD	$ 350,000	3/31/2025	No	No	No
22A14	University of Miami	Claes Wahlestedt, MD, PhD	$ 349,981	3/31/2024	No	No	No
22A15	University of Miami	Karen Nuytemans, PhD	$ 350,000	3/31/2024	No	No	No
22A16	University of Miami	Philip Harvey, PhD	$ 99,887	3/31/2023	No	No	No
22A17	University of South Florida	Hariom Yadav, PhD	$ 743,661	3/31/2026	No	No	No

1. **Grant #:** 22A01 *In vivo* Functional Analysis of MBLAC1: A Novel Genetic Risk Factor In Alzheimer's Disease With Therapeutic Potential

Principal Investigator: Randy Blakely, PhD

Organization: Florida Atlantic University

Abstract: Significant progress has been achieved in understanding the pathophysiological basis of Alzheimer's disease (AD) through the identification and study of rare, functional mutations in familial forms of the disease. Recently, we discovered an unstudied gene in *C. elegans*, termed swip-10, whose function in glial cells supports the health and signaling of nearby neurons *in vivo*. Current work with the model supports a "two-hit model" for the contribution of swip-10 to neuronal health, whereby mutation of the gene disrupts copper homeostasis, leading to altered mitochondrial metabolism and oxidative stress, leading to over-excitation that can drive neurons toward degeneration. Following this discovery, the team identified the gene Metallo-β-lactamase Domain-Containing Protein 1 (MBLAC1) as the likely swip-10 homolog in man and have published evidence that a loss of function mutation introduced into the mouse form of the gene produces metabolic stress *in vivo*. Recently, Genome-Wide Association Studies (GWAS) have identified MBLAC1 in a small cluster of genes linked to comorbid AD and heart disease with follow up studies revealing reduced MBLAC1

gene expression in postmortem AD brain, compared to healthy, age-matched controls. We suggest that the contribution of MBLAC1 to forms of AD with comorbid heart disease may reflect the intense energy demands characteristic of brain and heart. Importantly, a recent genetic study of the impact of a hereditary Presenilin1 (PSEN1) hereditary mutation linked to AD has revealed conspicuous changes in MBLAC1 gene expression in the brain, suggesting that MBLAC1 may function in a critical pathway that contributes to the pathophysiology of known AD mutations, further justifying an intense analysis of MBLAC1 protein mechanisms of cellular function and metabolism and the protein's potential as a new target for AD therapy. Importantly, we recently demonstrated that MBLAC1 protein is the major, if not sole target in the mouse brain for the FDA approved drug, ceftriaxone, a molecule reported by others to have neuroprotective activity, including in AD models. Our proposal will use an iterative approach, utilizing both *C. elegans* and mouse models, to more deeply characterize the biological mechanisms underlying the neuroprotective potential of MBLAC1 and its pharmacological targeting, including studies with both MBLAC1 and widely used mutant mice expressing AD mutations (e.g. PSEN1, Amyloid Precursor Protein), studies that we believe may lead to desperately needed therapeutic options for AD and its comorbidities.

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 #:** 22A02 Optimizing Rural Community Health Through Interdisciplinary Dementia Detection and Care (ORCHID)

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

Organization: Florida Atlantic University

Abstract: One in three older adults die with Alzheimer's disease; it kills more persons than prostate and breast cancers combined (Alzheimer's Association, 2021). In Florida, with the second-largest percentage of persons age 65 year and older nationally, earlier detection of Alzheimer's disease and related dementias (ADRD) is imperative. Early dementia diagnoses provide opportunities for modifying behaviors e.g. smoking, managing chronic conditions that contribute to ADRD risk, and initiating medications, which are more effective earlier in the disease process. Earlier detection also provides critical time to connect patients with community resources, and diminish caregiver burden. Although the primary care setting is well-suited for dementia screening due to long-standing relationships between providers and patients, low screening rates by providers reflect a combination of factors. These factors include unfamiliarity with updated cognitive assessment tools, lack of access to updated prevention and treatment protocols, and inaccurate perceptions that nothing can be done to help families facing a dementia diagnosis. This dementia detection and management gap is more severe in medically underserved areas, such as rural Florida's racially/ethnically diverse "Glades" region. The Ed and Ethel Moore Alzheimer's Disease Research Program will play a vital role in enabling us to address these disparities in dementia care in rural south Florida. Our consortium will investigate the hypothesis that creating a circle of community-based engagement among local academic,

clinical, and community resources will increase rates of dementia diagnosis and care management in a rural, racially/ethnically diverse underserved community. A multidisciplinary team of nursing students and faculty (Palm Beach State College), adult geriatric nurse practitioners (AGNP), and dementia researchers (Florida Atlantic University and University of Miami) will coordinate study activities with local providers and stakeholders. The long-range goal is to decrease costly preventable hospital admissions and early institutionalization. Specifically, nursing students will be trained to provide ADRD education and conduct cognitive screenings at senior housing facilities and faith-based organizations. Each student will be partnered with a community health worker, including local faith-based health educators. Positive screenings will be followed with visits by AGNPs in the research participant's dwelling or at the area hospital for cognitive assessments, who will communicate results to the resident's local provider. The providers will be offered a dementia diagnosis and management educational intervention based on a previously successful model (University of Miami), which includes guidelines for disclosing dementia diagnoses. Provider office staff will be offered an educational program using the new FDOH ADRD Resource Guide. To address caregiver burden, community health workers will complete the circle by assisting provider offices to connect patients and families to the Lake Okeechobee Rural Health Network – a coalition of mental health and social workers, health insurance experts, day services, and advanced care planners. Results will be compared with control and comparison provider or office staff groups who do not receive education and support. Applying this community-based participatory research design will facilitate translation of our findings back to caregivers, providers, and community agencies.

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.

3. **Grant #:** 22A03 Engineering Genetically Encoded Nanomachines to Block or Reverse Accumulation of toxic Amyloid Beta and Tau Oligomers

Principal Investigator: Robert Tomnk Jr., PhD

Organization: Florida State University

Abstract: Formation of toxic clumps of the proteins amyloid beta (Aβ) and tau is generally accepted to drive Alzheimer's disease (AD) development and progression. These clumps, called oligomers, cause neuronal cell death and further aggregate into the plaques and neurofibrillary tangles characteristic of AD. For reasons that are still poorly understood, these toxic oligomers are not efficiently delivered to the cellular machinery responsible for destroying misfolded or aggregated proteins. Improving delivery of these toxic oligomers to this machinery while sparing the normal, functional forms of Aβ and tau could potentially delay or even prevent development of AD with few or no side effects. Such a strategy could prove especially effective for high-risk patients (e.g., those with predisposing gene variants) when applied prior to the appearance of symptoms. ATP-dependent unfoldase-peptidase complexes such as ClpXP or the 26S proteasome mediate most cellular protein degradation. These complexes consist of a substrate-recruiting domain, an ATP-dependent unfoldase domain, and a barrel-shaped peptidase domain

that houses proteolytic sites in its center. After capture by the substrate-recruiting domain, the unfoldase domain extracts, unfolds, and translocates substrates into the core of the peptidase domain for destruction. In this pilot study, it will be tested whether we can re-engineer unfoldase-peptidases to selectively recognize and destroy AD-associated oligomers, both in a test tube using purified components, and in cultured neuronal cells expressing Aβ and tau. It is hypothesized that selective targeting of AD-associated Aβ and tau oligomers to unfoldase-peptidase nanomachines will enhance oligomer degradation and decrease cellular toxicity. To test this hypothesis, two Aims will be pursued. The research team will test whether substitution of the substrate-recruiting domains of several unfoldase-peptidases with oligomer-specific nanobodies (Nbs) supports the capture, unfolding, and degradation of AD-associated oligomers in a test tube model. It will be tested whether Nb-based targeting of AD oligomers to endogenous unfoldase-peptidases or to the engineered ones validated in Aim 1 reduces cellular toxicity to cultured neuronal cells. If successful, these pilot studies would validate a new therapeutic concept for the prevention or treatment of AD, and would justify more thorough preclinical testing en route to development of therapeutics for AD patients or those at 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.

4. **Grant #:** 22A04 Investigation of Therapeutic Effects of Neutral Sphingomyelinase Inhibitors on Tau Propagation In Different APOE Genotypic AD Patient-Derived iPSC organoids

Principal Investigator: Yang You, PhD

Organization: Mayo Clinic Jacksonville

Abstract: One of the hallmarks in Alzheimer's disease (AD) is the abnormal accumulation of tau proteins, known as tau tangles, in the brain. These tangled proteins tend to form harmful clumps in one region and spread to the others as seeds. Numerous studies indicate that tau accumulation would cause cell death and impair brain functions. In addition, the strongest AD risk factor APOE4, which is expressed in more than half of AD patients, was reported to markedly exacerbate tau-mediated neurodegeneration in a mouse model of tauopathy. Extracellular vesicles (EVs) are cell-derived small membranous vesicles, which have gathered great interest in studying AD with the capability of transferring pathogenic molecules including Tau. Therefore, blocking of EV biogenesis is potentially considered as a therapeutic target for AD. Notably, inhibition of EV generation with neural sphingomyelinase inhibitors, such as GW4869, were found to significantly halt tau propagation in PS19 tau mutant mouse model. Current studies also highlight that Apolipoprotein E (APOE) is involved in EV synthesis through its primary role as a lipid carrier. However, the therapeutic effects of neural sphingomyelinase inhibitors on targeting EV generation in AD, especially the potential difference between APOE3 and APOE4 genotypes, remains elusive. In this project, cortical organoids will be generated using AD-patient derived isogenic APOE3 and APOE4 iPSC lines. Abnormal tau proteins will be expressed in an individual organoid and then fuse that organoid with a normal one. Once the fusion is completed due to the migration of cells within organoids, the research team will

examine whether abnormal tau is spread from a tau-expressed organoid to a normal organoid. The Principal Investigator will also test if the AD risk gene APOE4 contributes to the spread of tau proteins using this organoids model. Next, the neutral sphingomyelinase inhibitors will be employed into the tau-expressed organoids to explore the differential effects on halting tau propagation between APOE3 and APOE4 genotypes. This research will develop a novel human brain-like model in the laboratory to study tau spread and identify whether inhibition of EV biogenesis may serve as a therapeutic target for AD. Further, it will help to provide fundamental insights into the precise medicine on AD with different APOE genotypes.

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 #:** 22A05 Developing A Digital Pathology and Machine Learning-Based Diagnostic Tool for Alzheimer's Disease and Related Dementia

Principal Investigator: Shunsuke Koga, MD

Organization: Mayo Clinic Jacksonville

Abstract: As the reliability of biomarkers continues to improve, neuropathologic assessment is critical to provide validation as the gold standard for diagnosing Alzheimer's disease (AD) and related dementias (ADRD); however, some challenges must be addressed. First, neuropathologic diagnosis is a time-consuming process that requires highly trained experts. Second, inter-rater variability between observers is unavoidable. Third, the number of neuropathologists has decreased globally. An increasing number of patients with neurodegenerative disorders makes it critical to have scalable, cost-effective means for post-mortem diagnoses to compensate for the decreasing number of neuropathologists. Digital pathology and machine learning (ML)-based approaches are attractive options. These methods hold great promise to improve the reproducibility of neuropathologic diagnosis and reduce the burden on neuropathologists. Nevertheless, the interpretation of the quantified data to generate a diagnosis still requires neuropathologic validation. It remains to be elucidated how to train an ML-based model to make a diagnosis of AD and non-AD tauopathies, such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's Disease (PiD), chronic traumatic encephalopathy (CTE), and globular glial tauopathy (GGT). To overcome this gap, we have developed an ML-based objective detection model for tauopathies to detect and quantify disease-specific tau lesions. Using these data, the burden of tau lesions in multiple brain regions was sufficient to differentially diagnose AD, PSP, CBD, and PiD with >95% diagnostic accuracy based on the random forest classifiers. Taken together, the combination of two different ML methods can be a practical diagnostic tool for tauopathies. The team aims to generalize the object detection model for tauopathies. To do this, the research team will immunostain sections of the motor cortex, caudate nucleus, and hippocampus with a phospho-tau antibody (AT8). The research team will also stain the hippocampus using 6F/3D antibody to assess amyloid-β pathology. The project will use 35 cases, including AD, PSP, CBD, PiD, and GGT, for training the model. Representative tau and amyloid-β lesions will be annotated in 100

images from each case, which will be used for training and cross-validation to develop an object detection model using the YOLOv3 algorithm. Secondly we aim to develop a diagnostic model based on quantitative measures in multiple brain regions. To do this, first the team will obtain quantitative burdens of each tau and amyloid-β lesion type in five brain regions (i.e., motor cortex, superior frontal gyrus, inferior temporal gyrus, hippocampus, and caudate nucleus) using the object detection model. Next the team will create random forest classifiers for diagnosing tauopathies using these quantitative data from 210 cases, including 40 each of AD, PSP, CBD, and PiD, 15 GGT, 10 CTE, and 25 non-tauopathy control. Successful completion of the resultant classifier will assist medical decision-making in the neuropathologic diagnosis of ADRD. To enhance translation to the clinic, the future goal will be to apply innovative object detection models to provide a quantitative burden of tau and amyloid-β lesions that will be critical to evaluating the impact on clinical course, antemortem neuroimaging, and genetics of tauopathies.

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 #:** 22A06 Brain Cell-Specific Epigenomic and Transcriptomic Impact of AD Risk Variants

Principal Investigator: Mariet Allen, PhD

Organization: Mayo Clinic Jacksonville

Abstract: The pathological hallmarks of Alzheimer's disease (AD) are the accumulation of cerebral plaques of β-amyloid peptide (Aβ) and intracellular neurofibrillary tangles. In additional neuronal cell loss and reactive gliosis are observed, much of which is mediated by microglia the primary immune cells of the brain. The role of microglia in AD can be beneficial or harmful, depending on the microglial sub-type, and activation state. Genome-wide association studies have identified more than 40 loci implicated in AD, which are overrepresented within regulatory regions of central and peripheral myeloid cells (monocytes, macrophages, and microglia). Collectively these findings indicate an important role for microglia in Alzheimer's disease. It is hypothesized that microglial molecular changes are associated with AD risk alleles and that identification of these changes can provide novel insights into disease pathogenesis. Key molecular changes previously implicated in AD and with AD risk variants include both epigenomic (gene regulation) and transcriptomic (gene expression) measures. These prior studies have largely been conducted on bulk brain tissue samples comprised of multiple cell types where associations with disease state (AD or control) or genetic variants (SNP genotypes) with individual cell types, or sub-types are challenging to derive. To capture the microglial-specific epigenome and transcriptome and differentiate microglial sub-types, single cell (sc) or single nucleu (sn) studies are needed. Technology has been developed to measure genome-wide gene expression (snRNAseq) and DNA accessibility (snATACseq) from single nuclei isolated from brain tissue. However, such studies have not yet been reported at large enough scale to assess the effect of low frequency AD risk variants on molecular changes in single cell-types such as microglia. This proposal aims to address this knowledge gap by capturing

snRNAseq and snATACseq measures from microglia isolated from post-mortem brain tissue selected based on genotype of targeted variants. The research team previously identified carriers of AD risk and protective alleles for low frequency variants at two loci implicated in microglial function, PLCG2 and ABI3. The research group demonstrated bulk brain expression changes in these genes in AD brains and mouse models. Now, the aim is to capture the landscape of DNA accessibility (ATACseq) and gene expression (RNAseq) in microglia isolated from brain tissue for carriers of these variants and individuals that do not carry either allele. Established analytic methods will be used to identify microglial molecular signatures, genes and networks, associated with these AD risk alleles. To validate findings in intact brain tissue RNA in situ hybridization (ISH) approaches will be used to evaluate microglia and key genes identified. The proposed study is expected to identify biological changes associated with genetic risk factors for AD in a specific cell type, microglia, which plays a critical role in disease pathophysiology. This knowledge can provide novel insights into microglial vulnerabilities that may be leveraged for development of therapeutic targets and strategies.

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.

7. **Grant #:** 22A07 The Role of Ufmylation for Alzheimer's Disease

Principal Investigator: Fabienne Fiesel, PhD

Organization: Mayo Clinic Jacksonville

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting more than five million individuals in the United States 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-β (Aβ) plaques and intracellular tau tangles. However, the molecular mechanism of that cause neurotoxicity and the accompanying pathological aggregation are not understood. Here, the research team wants to understand the role of ufmylation for AD. Ubiquitin Fold Modifier 1 (UFM1) is a ubiquitin-like small molecule modifier that similar to ubiquitin is attached to lysine residues of substrate proteins as a post-translational modification (ufmylation). Mutations that are associated with strong reduction of function in the genes that mediate the activation, conjugation, and ligation of UFM1 are all linked to severe neurodevelopmental disorders. Knockout of these genes in mouse models is embryonic lethal underscoring the importance of ufmylation for neuronal survival. While there is a strong premise for a neuroprotective role of ufmylation during development, the role of ufmylation for age-related neurodegenerative disorders is not yet established. The biological significance of ufmylation has only recently emerged and new roles are still being identified. UFM1 is involved several different key cellular pathways, among them the DNA damage response, the unfolded protein stress response, and the degradation of the endoplasmic reticulum via autophagy (ERphagy). Preliminary analysis of human postmortem brain suggests that several key components of the ufmylation cascade are reduced in AD brain

compared to controls. Further, data hint to a crosstalk of mitochondrial autophagy with the ufmylation pathway. Here, the research team will investigate the role of ufmylation for AD by expanding our analysis in human postmortem brain. The research team will also analyze the functionality of several ufmylation pathways in neuronal cell culture models to dissect which of these are impaired. As a result, our study will help to define the mechanisms of neurodegeneration and provide novel therapeutic targets and strategies for 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.

8. **Grant #:** 22A08 Apoe Genotype Effects on Cerebrovascular Integrity and Dementia-Related Pathology

Principal Investigator: Yasuteru Inoue. MD, PhD

Organization: Mayo Clinic Jacksonville

Abstract: Cerebral amyloid angiopathy (CAA) is characterized by cerebrovascular deposition of amyloid-beta (Aβ) and is found in the brains of over 90% of Alzheimer's disease (AD) patients. It is a major cause of damage to the critical barrier between the blood components and the brain tissue called blood-brain barrier (BBB) and spontaneous lobar hemorrhages. As the age of the population increases, the incidence of age-dependent CAA as well as AD is also expected to increase. However, currently there is no effective therapy to treat these diseases. As such, there is an urgent need to understand the molecular and cellular events leading to the onset and the progression of CAA and AD to inform therapeutic strategies. In this fellowship application, we plan to focus on addressing the pathogenic role of apolipoprotein E (apoE), whose gene APOE is the strongest genetic risk factor for AD, with APOE4 being the risky allele and APOE2 protective compared to the common APOE3 allele. Interestingly, both APOE2 and APOE4 are associated with increased risk and severity of CAA. ApoE is a major cholesterol carrier that supports lipid transport in the brain. In AD, apoE isoforms differentially impact both Aβ-dependent and Aβ-independent pathways. It is hypothesized that apoE modulates vascular pathways that affect BBB, cerebrovascular integrity, and dementia-related pathologies in an isoform-dependent manner. Specifically, it is planned to use 3D co-culture or cerebral organoid models that recapitulate anatomical and physiological properties of cerebrovasculature using patient-derived induced pluripotent stem cells (iPSCs) with APOE2, APOE3, or APOE4 genotype to investigate the impact of APOE produced by different brain cell types and vasculature on cerebrovascular integrity and CAA development. First, researchers will use iPSC-derived pericytes, endothelial cells (both are cerebrovascular cells), and astrocytes (cells in the central nervous system) co-culture model to study the effects of cell type specific APOE on cerebrovascular integrity. A 3D vascular organoid model will be employed to examine how expression of APOE isoforms affects vascular functions and CAA development. Second, researcners will treat iPSC vascular models with human plasma from individuals with different APOE genotypes to study if the APOE/lipoprotein from plasma affects vascular integrity. The result from this experiment will enable us to identify the blood-derived molecules that are either

detrimental or beneficial for vascular stability. Finally, human postmortem brains will be used with different APOE genotypes to isolate vascular cells and perform single-nucleus RNA sequencing. This will allow us to address molecular profiles in cerebrovasculature that are impacted by APOE genotypes. Upon successful completion of this project, we will have better understanding of how APOE genotype modulates vascular integrity and pathology in AD and CAA to inform mechanism-based 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.

9. **Grant #:** 22A09 Identification of Novel Genetic Risk Factors for Cerebral Amyloid Angiopathy and Characterization of the Implicated LINC-PINT Locus

Principal Investigator: Nilufer Ertekin-Taner MD, PhD

Organization: Mayo Clinic Jacksonville

Abstract: Alzheimer's disease (AD) is definitively diagnosed at autopsy by the presence of both extracellular amyloid plaques and intracellular neurofibrillary tangles. The primary constituent of amyloid plaques associated with AD, amyloid-beta peptide (Aβ), can also be found deposited in the brain cerebrovasculature; referred to as cerebral amyloid angiopathy (CAA). This pathology can lead to impaired blood vessel integrity and subsequent increased risk of brain hemorrhage, and dementia. CAA can occur as a distinct disorder where the primary site of amyloid deposition is in the cerebrovasculature, but is also a common finding at autopsy for neuropathologically confirmed AD patients. Presence of CAA at autopsy in AD patients has been associated with greater ante-mortem cognitive impairment, independent of the underlying AD neuropathological burden. Therefore, CAA is an important component of the dementia risk landscape for AD; identifying biological mechanisms that contribute to risk for CAA may lead to novel treatment strategies directed at reducing cognitive decline in AD patients with concurrent CAA involvement. Further, existing Aβ immunotherapies are not effective in clearing CAA. Moreover, patients with radiographic evidence of CAA are at increased risk of side effects from the now FDA-approved anti-Aβ therapy aducanumab. These findings strongly underscore the need to identify novel therapies and blood-based biomarkers for CAA. Established risk factors for the development of CAA include male sex and the APOEε4 AD risk allele. More recently, we identified a splice variant within the long non-coding RNA (lncRNA) LINC-PINT that decreases risk for CAA amongst AD cases that do not carry the APOEε4 allele. LINC-PINT levels are also elevated in AD brains and we discovered novel transcriptional pathways that correlate with brain LINC-PINT expression. The overarching goal of this proposal is to identify additional genetic risk factors for CAA overall and in the context of sex and APOE genotype, and translate these findings to the development of therapeutic targets and biofluid measures that relate to CAA and its radiographic biomarkers.We have previously collected genome-wide genotypes from 853 AD cases scored for CAA. It is proposed to collect genome-wide genotypes from additional individuals from the Mayo Clinic brain bank with neuropathological CAA scores and perform a genome-wide association study (GWAS) in this expanded cohort. To further increase statistical

power and translation to the broader population, we will findings will be evaluated together with those from a post-mortem population-based study with available genome-wide genetic and neuropathological CAA data. We expect to identify additional genetic risk factors for CAA, applicable to both AD patients, and the broader at risk population. The team will collect peripheral gene expression measures and targeted genotypes from enrolled dementia patients at the Mayo Clinic Florida ADRC that have brain imaging, to determine if the variants and genes implicated in prior studies (APOE and LINC-PINT), and those identified in aims 1 and 2, can translate to candidate peripheral biomarkers for CAA (aim 3). The proposal is expected to expand knowledge of the pathophysiology of AD and CAA, identify putative biomarkers.

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 #:** 22A10 Florida Consortium to Reduce Misinformation and Exploitation in AD

Principal Investigator: Nichole Lighthall, PhD

Organization: University of Central Florida

Abstract: Losses due to elder fraud have reached epidemic proportions. One in five Americans over age 65 are victims of financial exploitation, costing billions each year, with devastating consequences for wellbeing. A 2020 Federal Trade Commission (FTC) report revealed that Florida continues to have the highest incidence of fraud and financial exploitation compared to any United States' (US) state. Major contributors to this problem include the proliferation of misinformation campaigns and scams that target our rapidly expanding older population. Older individuals with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) are at heightened risk for exploitation due to disease-related neurocognitive changes, which is a particular concern in Florida – home to over 9% of US Alzheimer cases. Further, older adults' vulnerability to misinformation and online scamming increased during the COVID-19 pandemic, as safety requirements increased their reliance on digital technology to stay connected. This "perfect storm" was magnified in Florida's growing number of minority elders with cognitive impairments – many of whom faced isolation, limited resources, and lack of English fluency that further increased their vulnerability to misinformation and scams. Using a team science approach, the proposed consortium will utilize joint efforts at UCF, UM, and UF to fight fraud and the "infodemic" in Florida targeting older adults with AD and their families. The team's unique expertise in cognitive neuroscience of aging, clinical neuropsychology, and cybersecurity provides the necessary foundation to identify and address the primary drivers of exploitation among elders at risk for, and diagnosed with, AD. The project builds on foundational research showing that decline in frontal-executive functions characteristic of MCI and AD are crucial for the detection of deception. Also, poor inhibition promotes impulsive execution of irreversible actions or difficulty with complex decisions. Leveraging this prior knowledge, we will collect longitudinal data to identify and probe psychological and neural mechanisms involved in deception detection. The work also has genuine application: the team has developed behavioral, ecologically valid measures of fraud susceptibility and will use these novel methods

with standardized measures to identify diverse cognitively vulnerable individuals and develop effective intervention. The team science approach offers an unprecedented opportunity to address susceptibility to misinformation and exploitation among the most vulnerable. Achieving these goals can help to reduce health disparities, lessen caregiver burden, improve quality of life, and help individuals with AD age in place. The proposed consortium leaders (PI: Lighthall, UCF; Co-PIs: Levin, UM; Ebner, UF) are experienced investigators who have previously worked together on conceptually-related projects. The consortium will prospectively address this growing health crisis by leveraging behavioral assessments to pinpoint cognitive, affective, and social predictors of misinformation and exploitation susceptibility; identifying structural and functional neural circuitry involved in detection of misinformation and exploitation; developing strategic intervention for elders with cognitive impairment and caregivers to mitigate deception risk; and partnering with legal entities specializing in elder fraud as well as media liaisons in elderly residential living to promote culturally-sensitive intervention.

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 #:** 22A11 Novel Training In Interventions for Treatment Adherence in Underserved Diverse Patients at Risk for Alzheimer's Disease

Principal Investigator: Jeremy Grant, PhD

Organization: University of Florida

Abstract: Metabolic syndrome (MeSy) refers to a cluster of chronic health conditions that increase the risk of stroke and heart disease, including high blood pressure, high cholesterol, diabetes, and obesity. In addition to its effects on the body, MeSy has also been widely associated with increased risk for cognitive decline and Alzheimer's Disease (AD). It is shown that 55% of older adults in the United States are estimated to have MeSy, and this estimate is expected to increase in line with the country's increasingly aging population. Medication and healthy lifestyle modifications—including physical activity and dietary changes—are the frontline treatments for MeSy. However, treatment adherence rates remain low, and disability rates continue to rise. Notably, African Americans and Hispanics show disproportionately higher rates of MeSy as well as lower treatment adherence rates relative to White Americans. Identifying factors that contribute to poor treatment adherence among older adults with metabolic syndrome, particularly in ethnically-minoritized populations (MeSy), is essential. The research project will leverage an ongoing 1Florida Alzheimer's Disease Research Center (1FL ARDC) funded study examining psychosocial and cognitive risk factors for treatment adherence in older individuals with MeSy, as well as previously collected neuropsychological and neuroimaging data of the 1Florida ADRC to directly address the training goals for this fellowship. These training goals include: Learning the socio-cultural factors that influence the evaluation of patients and inform diagnostic accuracy, including reviewing best-practices literature in this domain while engaging and recruiting ethnically diverse research participants, developing hypotheses and methods in order to implement tailored interventions that mitigate AD

progression, developing protocols to receive Institutional Review Board (IRB) approval, and gaining expertise in advanced statistical analysis and public dissemination of research findings. Notably, the proposed training will also involve both empirical data collection and secondary data analysis. Under the supervision of his mentoring team, which has expertise in cross-cultural neuropsychology and interventions for cognitive decline, this fellowship will support Mr. Grant's developing expertise in Alzheimer's disease research and advancing his understanding of the social determinants of brain health. Furthermore, the existing infrastructure at the 1FL ARDC and facilities at the University of Florida will provide Mr. Grant with the tools to achieve his research aims, such as advanced neuroimaging techniques and access to experts in clinical care for older adults. This postdoctoral fellowship opportunity will culminate in a competitive submission of a K23 application to the NIA to design and implement novel behavioral interventions to prevent cognitive decline and Alzheimer's disease in older adults, improving and diversifying the number of highly trained patient-centered researchers.

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 #:** 22A12 Novel Behavioral and Neural Markers of Alzheimer'S Disease Progression: A Case for Visual Orienting

Principal Investigator: Adam Barnas, PhD

Organization: University of Florida

Abstract: Spatial navigation is an essential task, and the way in which we perceive our world relies on both the information that enters our senses and upon which aspects of the information we orient. Spatial navigation detriments are prevalent symptoms of Alzheimer's Disease (AD), resulting in limited mobility and decreased quality of life among patients and their caregivers. Typically, spatial navigation behavior is supported by visual navigation cues – signs, verbal instructions, and maps – that show the way to go. But before these cues can be useful, people need to find them, a task requiring two distinct aspects of attention: reorienting toward a particular kind of object and re-orienting to a location in space. Whereas AD patients show general deficits in attentional re-orienting, meaning that AD patients have trouble attending to objects and locations in visual space, individuals with Mild Cognitive Impairment (MCI) show specific deficits in space-based attention. It is hypothesized that deficits in attentional function underlie specific spatial navigation detriments among AD patients which manifest in distinct patterns of neural activity. This hypothesis will be addressed in two research aims: to determine the extent to which individuals with MCI show a deficit in space- and/or object-based attentional re-orienting; and examine connectivity between attentional neural network nodes underlying space- and object-based attentional re-orienting deficits in MCI. These research aims will directly link to two training goals: develop an empirical and theoretical background in AD pathology focusing on spatial navigation, visual attention, and general cognitive deficits and learn advanced fMRI techniques, including functional and structural connectivity and network analysis. The proposed research and training as part of this fellowship will leverage the existing

infrastructure from the ongoing grant FDOH 21A09 on ameliorating age-related decline of spatial navigation success. Under supervision of the mentoring team, which has non-overlapping expertise in spatial navigation, neuroimaging, experimental aging, and clinical neuropsychology/AD, Dr. Barnas will acquire profound knowledge in clinical research conduct and advance his neuroimaging analysis toolkit. Dr. Barnas compliments the expertise of the mentoring team by providing expertise in visual attention and psychophysics. The University of Florida offers a strong research and training context for Dr. Barnas' clinical fellowship via access to extensive clinical and basic science resources (e.g., through courses and workshops offered by the CTSI) as well as training in grantsmanship (e.g., UF's K-college). This clinical fellowship opportunity will allow Dr. Barnas to increase his publication record in clinical psychology, neuroimaging, and cognitive aging science and, crucially, the collection of preliminary data for a competitive submission of his NIH K99/R00 in 2022 to design and implement a training intervention toward improving attentional processing subserving spatial navigation skills in MCI and AD. In these efforts, this project has tremendous potential for basic science, translational, and clinical training-related impact, providing significant advancements to our understanding of brain-mediated function and dysfunction in AD and toward the development of empirically grounded and theoretically motivated rehabilitation intervention that ameliorates attention deficits in persons with 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.

13. **Grant #:** 22A13 Characterization of New CamK2-Tau Strains of Mice to Model Dementia

Principal Investigator: Jada Lewis, PhD

Organization: University of Florida

Abstract: Mutations in human tau cause a form of dementia that shares symptoms and pathology with the more common form of dementia known as Alzheimer's disease (AD). In the years following the discovery of these mutations, several laboratories, including ours, have generated transgenic mice that express the normal and mutant forms of human tau. One of the most widely used models was developed by my lab (Lewis lab), in collaboration with others, and is based on a system that requires two different strains of transgenic mice to be bred to each other, to create what we call bigenic mice. The lab name for this model is rTg4510 and it was created when a mouse that was transgenic for CamK2-tet-transactivator (tTA) is mated to a mouse that has the transgene for tet promoter-tau (tau). In this bigenic model, the human tau is expressed specifically in the forebrain, by virtue of the CamK2 promoter. Although this mouse model appears to be an excellent mimic of some key features of human disease, we have recently learned that the transgene used to produce this mouse model integrated into the host genome in a way that disrupted several important genes. Additionally, because the rTg4510 model requires breeding two independent strains of mice, any study in which investigators may want to breed in other genes implicated in dementia becomes costly, cumbersome and inefficient. Other commonly used models of tau dementia use a transgene vector system based

on the mouse prion protein gene promoter. These mice also mimic aspects of human disease, but because the transgene is expressed broadly throughout the nervous system, the mice then develop a motor neuron disease that paralyzes them (a symptom that is not associated with human dementia). To overcome these problems, the research team has constructed new lines of mice in which we have directly linked the CamK2 promoter to normal (wild-type or WT) or mutant human tau (P301L and P301S). There are multiple lines of mice that express human tau at different levels. We now propose studies to characterize the ages at which the mice develop abnormal tau inclusions that are the defining pathologic feature of tau dementia. The team will determine whether and when the models begin to show neuronal death or atrophy. The team will determine the age at which the mice begin to show reductions in cognitive function. Finally, we will determine the susceptibility of each of these lines of mice to prion-like seeding by tau aggregates enriched from human AD brain. Collectively, these studies will provide the types of detailed characterization that are required to widely distribute these new models as translational tools for drug discovery and testing.

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 #:** 22A14 The Beneficial Role of Exercise-Induced Neuronal DNA Damage in Aging and Alzheimer's Disease

Principal Investigator: Claes Wahlestedt, MD, PhD

Organization: University of Miami

Abstract: Each year, nearly one in three seniors (adults age 65+) in the U.S. dies with Alzheimer's disease (AD) or other related dementias. Florida has a disproportionally high number of seniors, 80% of which have at least one chronic condition impacting their quality of life. One of the many pathologies that links AD and other chronic diseases of aging is accumulation of deoxyribonucleic acid (DNA) damage in tissues throughout the brain and body. Aerobic exercise is a safe, affordable, and accessible intervention that has consistently demonstrated its potential to decrease the risk of AD and co-morbidities associated with a sedentary lifestyle. Interestingly, it is known that aerobic exercise acutely induces DNA damage in peripheral tissues including muscle, liver, and blood cells. This paradox prompts the question: how does exercise prevent chronic disease, stave off cognitive decline, and extend healthspan? We hypothesize that exercise-induced DNA damage is a necessary stressor that upregulates DNA damage repair processes in peripheral tissues and in the brain. Research in the field of hormesis generally supports this hypothesis, concluding that acute biochemical stress is necessary to improve cellular function (e.g., fasting). However, the mechanistic link between exercise-induced DNA damage in the brain, long-term neuroprotection, and DNA-damage related peripheral biomarkers of healthy aging is unexplored. Our preliminary data shows that multiple DNA damage repair enzymes are upregulated in the brain of mice post-exercise. Until recently, sensitive methods to detect the most common type of DNA damage, single-stranded DNA breaks (SSBs), did not exist. Efforts from our team and collaborators have led to the

development of a next-generation sequencing method that allows for spatial detection of SSBs throughout the genome, referred to as SSiNGLe. This is important because DNA damage does not occur randomly. Indeed, depending upon the stimulus or the cell type, unique SSB signatures can be characterized. When SSiNGLe was applied to blood cells from human subjects of various ages, we were able to derive a "breakome age" based on the frequency of breaks at specific locations in the genome. Such a breakome profile can plausibly serve as an early biomarker to differentiate healthy aging from diseased aging. With all of this in mind, we will investigate the relationship between exercise-induced DNA damage and neuroprotection in aging wild-type and AD mice. Characterizing the post-exercise DNA damage response in the blood and brain at various ages will allow for the establishment of a blood-based biomarker that tracks how exercise influences cognition in both healthy and AD mice as they age.Innovation and Significance: While there is a clear benefit of aerobic exercise to AD and its co-morbidities, deep mechanistic insight of the paradoxical role of DNA damage in brain aging is missing. Emerging technologies like SSiNGLe combined with established, albeit less sensitive methods, will reveal new insight into the mechanisms of healthy and diseased aging in both the brain and blood. These studies will help establish a novel biomarker of exercise response and aging in the context of DNA damage, and provide a novel modality for the assessment of potential therapies that promote a healthy aging profile.

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 #:** 22A15 Characterization of African American Alzheimer Disease GWAS Hit RBFOX1

Principal Investigator: Karen Nuytemans, PhD

Organization: University of Miami

Abstract: Compared with individuals of European descent, African American individuals from the same community are approximately twice as likely to develop Alzheimer disease (AD). Despite this disparity, the largest Alzheimer disease genome-wide association studies (GWAS) so far have been conducted in individuals of European descent. A recent meta-analysis in African American cohorts identified 11 novel loci for AD in this population, including a region at chr16p13 (odd ratio=3.8) located between RNA Binding Fox-1 Homolog 1 (RBFOX1) and Transmembrane Protein 114 (TMEM114) [Kunkle et al. 2021]. Interestingly, lower expression of RBFOX1 as well as RBFOX1 intronic variants have also been reported to be associated with brain β-amyloid load in autopsy material of individuals of European ancestry [Kunkle et al. 2021, Raghavan et al. 2020]. The RBFOX1 protein is highly expressed during neuronal development, is active in the nucleus and cytoplasm and believed to be involved in RNA splicing and stability respectively in these locations; with putative direct and indirect effects on processing of AD gene APP and synaptic transmission in the brain [Alam et al 2014, Voung et al 2018, Lee et al 2016]. Together these data indicate RBFOX1 and its surrounding GWAS locus are a good candidate for functional follow-up in AD pathogenesis, regardless of ancestry. Therefore, we propose a two-pronged investigation: Characterize RBFOX1 function in AD relevant context. To

directly assess RBFOX1 function in neuronal development and characteristics of AD neurons, the research team will knockdown and overexpress RBFOX1 in induced pluripotent stem cell (iPSC)-derived neuronal progenitor cells (NPC) of an African American control using viral transduction of shRNAs (downregulating expression) or overexpression plasmids. After quality control of transduction efficiency, these NPCs with different levels of RBFOX1 expression will be differentiated in neurons and characterized for general morphology (e.g. neurite outgrowth) and AD-relevant phenotypes (e.g. Aβ and tau levels). The team will also perform transcriptome analysis studying downstream effects on RNA processing of AD relevant genes first, and all genes second. Characterize genomic region surrounding the genome-wide association study (GWAS) hit for regulatory potential. The chr16p13 GWAS variant and it's linkage disequilibrium block is located in a noncoding region, indicating regulatory function such as long range enhancer or silencer activity, as underlying mechanism of the signal. Publicly available data will be used on histone modifications, chromatin interactions and transcription factor binding sites in AD affected brain regions to prioritize regions of interest within the GWAS peak area. For those variants and/or regions with regulatory potential we will perform 'tiled' Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) interference/activation assays – blocking or increasing regulatory activity – in iPSC-derived neurons across the region and assess AD-relevant phenotypes as well as expression of candidate target genes to pinpoint the variants driving the association signal and their target gene(s) if not RBFOX1. Smaller expression changes of genes in specific pathways could have a significant influence on when or how disease starts or progresses. The identification of novel gene/pathways and functional noncoding variants (for screening purposes) in AD can lead to novel entryways in treatment of AD delaying onset or progression of disease. The identification of these for the African American population will help reduce the health disparity for this population.

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 #:** 22A16 Postdoctoral Fellowship In Neuropsychology and Cognitive Health

Principal Investigator: Philip Harvey, PhD

Organization: University of Miami

Abstract: Promoting cognitive health and functional independence among the vast growing older adult population is a key national priority. Promising data has emerged concerning the effectiveness of targeted cognitive training interventions to improve the cognitive abilities and functional outcomes of older adults, which are essential to independent living. The research group of investigators at the Center for Cognitive Neuroscience and Aging (CNSA) are experts in the early detection of cognitive change in persons at-risk for the development of Alzheimer's disease (AD) and AD related neurodegenerative disorders. In addition, Primary Mentor, Dr. Philip Harvey and Co-Mentor Dr. David Loewenstein are experts in functional skills training and have co-developed real-world functional task simulations. The vast experience with the development and delivery of cognitive training interventions to older adults representing diverse

ethnic/cultural groups is central to the unique postdoctoral fellowship training opportunity. The proposed one-year postdoctoral research fellowship will offer an individual with a doctoral degree in neuropsychology the opportunity to receive specialty training in AD and AD related disorders. This fellowship training will result in the development of advanced skills in clinical, cognitive, and functional assessment, research methodology, grant writing, psychometric test development, and cognitive remediation, in a diverse sample of older Floridians who are at-risk for developing neurodegenerative disorders. A unique training emphasis will include the delivery of empirically supported cognitive interventions with the aim of improving brain health. The fellow will learn about which intervention strategies have the potential to slow decline and optimize cognitive function. Candidates will be expected to generate an independent project that can be piloted in our Center and submit a training award or other grant application upon completion of the postdoctoral fellowship year. The mentorship team is highly experienced and integrated and have 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 cognition, aging, functional skills training and the neurosciences. Dr. Rosie Curiel Cid, David Loewenstein, and Marcela Kitaigorodsky, all of whom are core CNSA faculty, would serve as secondary mentors. Each mentor offers unique but complementary experience. The University of Miami Brain Health Pavilion and the large NIH-funded clinical research program at the CNSA will serve as the training environment.

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 #:** 22A17 Role of Microbiome in Aging of Gut and Brain in Floridian Older Adults

Principal Investigator: Hariom Yadav, PhD

Organization: University of South Florida

Abstract: Alzheimer's disease (AD) is an age-related progressive neurodegenerative disease and became a debilitating public health problem in older adults. AD is characterized with higher accumulation of amyloid beta and tau proteins in the neurons resulting dysfunction and death in neurons, which in turn cause cognitive decline and dementia. Clinical trials to treat AD have highest failure rate, indicating novel strategies are needed to combat the cognitive decline/AD. Several preclinical studies demonstrates that the early interventions are successful to slow and/or ameliorate the progression of cognitive decline and AD. However, non-invasive, inexpensive, easy to follow-up and clinically validated prognostic markers for early detection of cognitive decline and AD are not known. Thus, developing such markers which can be frequently measured with least burden in the older adults are highly required.Here, we hypothesize that the microbiome-based biomarkers can differentiate cognitive decline and dementia from healthy; and can predict progression of cognitive decline older adults. We base our hypothesis on the facts that trillions of microbes (microbiome) living in our gut contributes in brain health through modulating gut-brain axis. Multiple emerging evidence shows that abnormalities in gut including microbiota, leaky gut and inflammation are linked with cognitive

decline in older adults. However, these conclusions are derived from either small single center clinical studies and/or rodent analyses. In addition, no prospective follow-up longitudinal studies are done to determine the early prediction of AD risk based on microbiome and gut related phenotypes. To address, these important gaps-in-knowledge, herein we proposed a large multi-center study to enroll ~400 older adults within the Florida state, to develop and validate microbiome-based biomarkers to predict the risk of AD/cognitive decline in older adults. We plan to investigate following specific aims: to develop and validate a model to determine if microbiome signature differentiates mild cognitive impairment (MCI) and dementia from healthy; and metabolites, leaky gut and inflammation can strengthen the power of model. Additionally, to determine if microbiome signature can predict progression of cognitive decline in older adults, and metabolites, leaky gut and inflammation can strengthen this prediction. Impact and future perspectives: it is expected to establish a proof-of-concept that if the microbiome-based biomarkers will predict risk of cognitive decline and AD in older Floridians. Our study is first-of-its kind in Florida state which exclusively focused on determining the role of microbiome in older Floridians with novel perspective longitudinal follow-up study design and easily implementing measures that are supported with well-established protocols and expertise of multi-disciplinary team from established and under-representative to conduct the high-quality grant-supported research institutes/centers in Florida.

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 B
Fiscal Year 2020-2021 Active Grants
(Funding Year 2020-2021)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
21A01	Florida Atlantic University	Monica Rosselli, PhD	$ 99,051	2/28/2023	No	Yes	No
21A03	Florida Atlantic University	Howard Prentice, PhD	$ 99,050	2/28/2023	No	No	No
21A04	Florida Atlantic University	Qi Zhang, PhD	$ 247,620	2/28/2025	No	Yes	No
21A05	Florida State University	David Meckes, PhD	$ 99,051	2/28/2023	No	No	No
21A06	University of Central Florida	Suren A. Tatulian, PhD	$ 247,620	2/28/2025	No	Yes	No
21A07	University of Florida	Yong Ran, PhD	$ 247,620	2/28/2025	No	No	No
21A08	University of Florida	Karen N McFarland, PhD	$ 99,051	2/28/2023	No	No	No
21A09	University of Florida	Steven M. Weisberg, PhD	$ 247,613	2/28/2025	No	No	No
21A10	University of Florida	Stefan, Prokop, MD	$ 246,991	2/28/2025	No	No	No
21A11	University of Florida	Barry Setlow, PhD	$ 247,620	2/28/2025	No	No	No
21A12	University of Florida	Karina Alviña, PhD	$ 99,051	2/28/2023	No	No	No
21A13	University of Miami	W. Dalton Dietrich, PhD	$ 247,620	2/28/2025	No	No	No
21A14	University of Miami	Coleen M. Atkins, PhD	$ 247,620	2/28/2025	No	No	No
21A15	University of Miami	Claes Wahlestedt, MD, PhD	$ 247,542	2/28/2025	No	No	No
21A16	University of Miami	Bonnie E. Levin, PhD	$ 99,051	2/28/2023	No	No	No
21A17	University of Miami	Holly N. Cukier, PhD	$ 247,620	2/28/2025	No	No	No
21A18	University of Miami	Katrina Celis Delgado, MD	$ 99,051	2/28/2023	No	No	No
21A19	University of Miami	Rosie Curiel Cid, PsyD	$ 86,615	2/28/2023	No	No	No
21A20	University of Miami	Tatjana Rundek, MD PhD	$ 247,620	2/28/2025	No	No	No
21A21	University of Miami	Grace Zhai, PhD	$ 247,620	2/28/2025	No	No	No
21A22	University of Miami	David Loewenstein, PhD	$ 88,466	2/28/2023	No	No	No
21A23	University of South Florida	Mark S. Kindy, PhD	$ 247,620	3/31/2023	No	No	No
21A24	University of South Florida	Laura J. Blair, PhD	$ 247,620	4/30/2025	No	No	No
21A25	University of South Florida	Nan S. Park, PhD	$ 80,000	2/28/2023	No	No	No

1. **Grant #:** 21A01 Postdoctoral Research Fellowship in Neuropsychology and Brain Biomarkers of Abnormal Aging

Principal Investigator: Monica Rosselli, PhD

Organization: Florida Atlantic University

Abstract: During this reporting period, the research fellow has been completing and/or making progress in the following aspects: preparing papers for publication (see list of co-authored publications below), which includes the reviewing and analyzing background literature and

determining methodological procedures; preparing data for analysis, analyzing data and writing up results, collaborating on writing, editing, and preparing co-authored manuscripts for submission. Research staff also continued training on theoretical issues and analysis of brain biomarkers' data obtained from volumetric brain measures, amyloid beta depositions in the brain, including visual reading of amyloid positivity in positron emission tomography (PET) scans and atrophy on Magnetic Resonance Imaging (MRIs), levels of neurofilament light in the blood, and reviewing relevant literature. The team continued training on case revision and preparation of case reports for publication and writing the first case report. Acquired knowledge on data storage and managing systems for clinical, neuropsychological and biomarkers (Epic, Synapse, Redcap, CATE FIU lab). Preparing cases for presentation in biweekly clinical consensus conferences which includes: reviewing patient data and selecting cases based on pre-established criteria. This includes preparing relevant information including patient history; neuropsychological tests scores, biomarkers, and MRI and PET scans images, brain volumes, NfL and genetic information.

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

Collaborations: None at the time of reporting.

Journals: Rosselli, M., Velez Uribe, I., Ahne, E., & Shihadeh, L., (2021). Culture, Ethnicity, and Level of Education in Alzheimer's Disease (Manuscript submitted for publication). Department of Psychology, Florida Atlantic University.

Arruda, F., Rosselli, M., Kurasz, A.M., Loewenstein, D.D., DeKosky, S.T., Lang, M., Conniff, J., Vélez Uribe, I., Adjouadi, M., Rodriguez, M.J., Greig, M.T., Barker, W., Curiel, R.E., Duara, R. (2021) Stability in Cognitive Classification as a Function of Severity of Impairment and Ethnicity (Manuscript submitted for publication). Department of Psychology, Florida Atlantic University.

Greig M.T., Lang, M., Barker, W., Arruda, F., Vélez Uribe, I., Conniff, J., Loewenstein, D.A., Duara, R., Adjouadi, M., Gonzalez, J., Rodriguez, M.J., Curiel, R.E., and Rosselli, M. (2021) The Association of Depression and Apathy with Alzheimer's disease Biomarkers in a Cross-Cultural Sample (Manuscript submitted for publication). Department of Psychology, Florida Atlantic University.

Pollock, S., Velez Uribe, I., & Rosselli, M. (2022) The Effect of Language Experience and Gender on Performance on Verbal Fluency Tests. Abstract accepted. To be presented at the conference of the International Neuropsychological Society (INS), New Orleans, February, 2022.

Patents: None at the time of reporting.

2. **Grant #:** 21A03 Role of Hypoxia in Triggering Alzheimer's Disease Pathogenesis: Sulindac as a Potential Therapeutical Intervention

Principal Investigator: Howard Prentice, PhD

Organization: Florida Atlantic University

Abstract: Alzheimer's Disease (AD) continues to be the most prevalent form of senile dementia without any significant therapy. Oxidative damage and mitochondrial dysfunction are accepted as major factors responsible for hypoxic injury and AD pathogenesis, but there are no effective

therapeutic strategies to utilize these mechanisms for the development of new drugs. Hypoxia was shown to elicit increased production of β amyloid (Aβ) and dysfunction in tau proteins which also leads to neuronal death by increasing ROS formation. Research staff have been interested in upregulating the mechanisms that cells use to protect against oxidative damage and have reported that the anti-inflammatory drug (NSAID) sulindac can protect the heart against ischemia/reperfusion (I/R) damage by initiating a protective preconditioning response, independent of its NSAID activity. Because of its unique properties, sulindac was selected by the National Institute of Aging for testing as a drug for life span extension in mice in their Interventions Testing Program. This team proposes to investigate the role of hypoxia in Aβ aggregation and tau hyperphosphorylation in *in vitro* and *in vivo* AD model. One goal is to test the effect of sulindac, a preconditioning agent on reverting the hypoxia induced AD pathogenesis. Upregulating protective pathways against oxidative damage can improve the effectiveness of AD therapeutics. These studies, if successful will be the first to show therapeutic potential of sulindac in slowing down the development of AD. Staff propose to understand the role of hypoxia in amyloid accumulation, hyperphosphorylated tau proteins and to test the protective effect of sulindac.

Ongoing experiments will address characterizing the pattern of aggregation of the Aβ secreted by SHSY-5Y APP overexpressing cells under hypoxia. The team will utilize SHSY-5Y cells overexpressing amyloid precursor protein (APP) for these studies which is an accepted *in vitro* AD model. The team will characterize the pattern of Aβ aggregation secreted by SHSY-5Y APP overexpressing cells by measuring Aβ aggregation and cell survival under normal and hypoxic conditions. Staff will test the effect of sulindac on Aβ aggregation and cell viability in control and hypoxia conditions, and also investigate the role of hyper-phosphorylation of tau protein under hypoxic conditions with and without the treatment of sulindac.

The research team also set out to test the effect of chronic treatment with sulindac in Aβ aggregation in an AD mouse model when subjected to hypoxia. Research staff will use the APP23 mouse model that is extensively used and characterized for AD. In these experiments, researchers will investigate whether hypoxia accelerates Aβ formation by histopathology and if this could be reverted by sulindac and measure Aβ aggregates in both CSF and brain extracts, and then determine if sulindac treatment alters Aβ aggregation. It will be determined whether hypoxia treatment accelerates cognitive impairment in transgenic mice and if this could be reversed by sulindac.

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.

3. **Grant #:** 21A04 Rebalancing Brain Cholesterol – A Novel Therapeutic Strategy for Alzheimer's Disease

Principal Investigator: Qi Zhang, PhD

Organization: Florida Atlantic University

Abstract: Research staff will examine the role of mChol and APP in synaptic vesicle (SV) turnover and neurotransmitter release. First, staff used cultured hippocampal neurons from beta-amyloid precursor protein (APP)-knockout mice and wildtype control. To do so, staff used a refined Filipin staining protocol to compare mChol in those two groups of cells and indeed found a significant reduction of surface mChol in the knockout cells. Second, a new mChol reporter was used to examine live-cells and found that such surface mChol reduction is a compensatory response to the slowdown of mChol turnover especially at axon terminals that experience much high rate of membrane turnover (due to synaptic vesicle exo-/endocytosis). This finding was confirmed by Filipin staining at selected time points in fixed cells and generalized polarization imaging that indirectly measure mChol change in live neurons. Third, staff co-imaged fluorescent reporters for mChol, APP, and synaptic vesicles. It was found that SV turnover leads to surface mChol increase and triggers APP-mediated mChol recycling. When APP is absent or mutated, mChol recycling is significantly delayed, causing an accumulation of mChol on surface membrane and/or early endosomes.

Elucidate how APP cleavage affects mChol homeostasis, SV turnover, and neurotransmitter release. Using the fluorescent reporters for APP and mChol, the team is studying their turnover upon the application of specific inhibitors for a/b/g-secretases. The most profound changes are observed in cells treated with g-secretase inhibitor, which is a significant reduction of total mChol. a- or b-secretase inhibitors showed very little impact on mChol distribution, but did cause significant redistribution of uncleaved APP. Consequently, staff has found that only g-secretase inhibitor affects SV turnover and synaptic transmission under prolonged stimulation. The team continues to investigate how proteolytic fragments of APP affect mChol, SVs and synaptic transmission.

Evaluate the pathological contributions of APP mutations and mChol dysregulation. The team just started experiments for this specific aim using aging littermates bearing all three genotypes of APP (+/+, +/-, and -/-). Researchers are collaborating with Dr. Lei Liu to examine changes of synaptic vesicle proteins, gliosis and Tau hyperphosphorylation using Western blot and enzyme-linked immunoassay (ELISA). The team has obtained RNA-seq data and are analyzing gene expression changes in APP-null and wildtype mice at different age groups. Moreover, the team is learning tissue cleaning techniques and will use a new light-sheet microscope in Florida Atlantic University's imaging-core to examine neuronal connectivity, pathology and degeneration in transgenic mouse brain. Last, but not the least, brain tissues have been collected from different groups of mice at different ages, and will use mass spec to measure their Chol contents.

In summary, the research team has made steady progress on all three specific aims. The team is optimistic that the proposed research goals will be met on time.

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

Collaborations: Postsecondary educational institutions involved: Harvard University; We have built collaboration with Dr. Lei Liu at Harvard University. Dr. Liu, an expert in Alzheimer's disease genetics and protein assays, has been working close with us to assess changes in APP, secretase, synaptic proteins, and all AD-related gene expression changes using both biochemical and genomic methods.Number of students receiving training or performing research under the research project: 5.

Journals: Alamgir, S., Pelletier, O. B., Thomas, D., Rubio, V., Stawikowski, M. J., Zhang, Q. Measuring Membrane Lipid Turnover with the pH-sensitive Fluorescent Lipid Analog ND6. J. Vis. Exp (173), e62717, doi:10.3791/62717 (2021).

Patents: None at the time of reporting.

4. **Grant #:** 21A05 Mesenchymal Stem Cell-Derived Extracellular Vesicles for the Treatment of Alzheimer's Disease

Principal Investigator: David Meckes, PhD

Organization: Florida State University

Abstract: Alzheimer's Disease (AD) is an irreversible and progressive brain disease that affects over five million Americans. The disease slowly destroys cognitive functioning, the ability to carry out the simplest tasks, and eventually death. AD is the most common form of dementia in the elderly and despite decades of research, the molecular and pathophysiological causes of the disease remain unknown, with no effective treatments. As the American population continues to age and AD becomes more prevalent, it is imperative that researchers investigate novel therapeutics to slow or stop disease progression. A recent study reported that "healthy" extracellular vesicles (EVs) injected into diseased mice (an Alzheimer's mouse model) trap amyloid-beta (Aβ) protein, a key determinant of pathological plaque formation in the brains of Alzheimer's patients. Further studies describe the importance of EVs in Aβ clearance from the brain. In light of these new and exciting findings, this team will investigate the proposed effects of "healthy" EVs on preventing AD formation in preclinical models. In this study, the team proposes to utilize EVs from mesenchymal stem cells (MSC) which have been shown to possess anti-inflammatory and neuroprotective properties. Using a novel 3D aggregate culture system (patent pending), researchers have found elevated production of EVs with enhanced anti-inflammatory and neuroprotective properties under these growth conditions. Therefore, the team will administer EVs produced with this system to AD mice and monitor plaque deposition, learning and memory. The team will further enhance the neuroprotective properties of the EVs by loading EVs with specific proteins, compounds or RNA cargo. If our predictions are met, the implications for treatment of AD would be truly groundbreaking.

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 #:** 21A06 Amyloid Beta Oligomers' Structure, Membrane Pore Formation, and Toxicity

Principal Investigator: Suren A. Tatulian, PhD

Organization: University of Central Florida

Abstract: Progress has been made towards to identify membrane pore formation by various Amyloid beta (Ab) species using lipid membranes mimicking the plasma and mitochondrial

membranes, as well as isolated mitochondria. Spectroscopic studies have been conducted to determine the structure of Ab1-42 in lipid membranes mimicking cell plasma membranes. Circular dichroism (CD) spectra were measured at 20oC and 37oC. Spectra of Ab1-42 in aqueous buffer generated a deep minimum at 218-220 nm at both temperatures, indicating formation of b-sheet structure. CD spectra of Ab1-42 reconstituted in lipid vesicles displayed deeper minima at 215-216 nm, again indicating formation of b-sheet structure. The blue-shifted CD bands of the peptide in membranes suggest twisting of b-strands to a larger degree. Twisted b-strands are typical for b-barrel protein structures, which form pores in cell membranes. Thus, CD data suggest formation of b-barrel-like structure by Ab1-42 in lipid membranes.

Fluorescence spectroscopy was used to see whether the emission wavelength and/or intensities change upon incorporation of the peptide in lipid membranes. Excitation at 220 nano meter (nm) resulted in relatively sharp emission peaks at 310 nm for Ab1-42 in buffer or in vesicle membranes, with higher intensity in the latter case. This finding indicates that the peptide is inserted into the membrane, which protects from fluorescence quenching by water. Stronger signal at 220 nm in the presence of vesicles results from light scattering. Thus, CD and fluorescence data suggest that Ab1-42 does insert into lipid vesicle membranes and adopts b-sheet structure with twisted strands.

The main information on secondary structure and orientation of Ab1-42 relative to the membrane was obtained from polarized attenuated total reflection Fourier transform infrared (ATR-FTIR) experiments. These experiments were conducted on peptide-lipid samples in dry state and after addition of aqueous buffer, at 1:50 peptide/lipid molar ratio. ATR-FTIR spectra were measured at parallel (II) and perpendicular (^) polarizations of the incident light, and peak-fitting was applied to identify the spectral components in the lipid carbonyl and peptide amide I and amide II regions. Spectral analysis indicated that a-helical and b-sheet fractions, i.e., amide I components at 1658 cm-1 and 1631 cm-1, in Ab1-42 in dry state are fa = 0.24 (10 amino acid residues) and fb = 0.30 (12.6 amino acid residues). A significant fraction of turn structure (ft = 0.41) and a negligible fraction of unordered structure (fr = 0.052) are also present. Overall, these studies identify the secondary structure and the orientation of Ab1-42 reconstituted in lipid membranes, which will lead to determination of the structure of ion-conducting membrane pores that play a role in Ab neurotoxicity.

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

Collaborations: None at the time of reporting.

Journals: Abedin F, Kandel N, Tatulian SA. Effects of Aβ-derived peptide fragments on fibrillogenesis of Aβ. Scientific Reports, 11(1):19262, (2021) doi: 10.1038/s41598-021-98644-y.

Patents: None at the time of reporting.

6. **Grant #:** 21A07 Function of Chimeric Phagocytic Receptor Targeting Aβ and Tau Protein

Principal Investigator: Yong Ran, PhD

Organization: University of Florida

Abstract: Alzheimer's disease (AD) is the most common form of dementia among the elderly. Over five million Americans currently have AD, and the number of cases is expected to rise to

>13 million by 2050. No effective AD therapies exist, and many aspects of AD pathogenesis remain enigmatic. AD is hypothesized to be proteinopathies. Despite the growing understanding of the pathogenic mechanisms underlying these disorders, progress with respect to development of new therapeutics has been lagging. Based on the premise that protein aggregation and accumulation in AD and many other neurodegenerative disorders is a key, causal, pathologic event, it is logical to pursue therapeutic strategies to i) prevent aggregate formation ii) enhance clearance of the aggregate or iii) neutralize "toxic" signaling by the aggregate. Many strategies targeting protein aggregates have been developed, but these strategies have proven difficult to translate, or in some cases, found to have dose limiting side-effects. Further, even in the preclinical studies supporting clinical development, most of these therapeutic approaches have shown modest effects. Robust effects may have been reported from prophylactic or early interventions studies, but evidence for efficacy is much more limited, or absent, for treatment studies initiated when pathology is widespread.

Enhancing clearance of the target protein via phagocytic mechanisms is arguably the most direct way to test the hypothesis that enhancing clearance will be beneficial. Here, staff will directly evaluate this premise using novel chimeric phagocytic receptors (CPRs). These studies are analogous to chimeric antigen receptor T-cell (CAR-T) studies, but instead of engineering T-cells to target a specific protein, they will harness phagocytic cells to target either Aβ or tau. The team has already created and functionally validated multiple CPRs targeting Aβ and tau. These CPRs are fusion molecules composed of an extracellular single chain variable fragment (scFv) that binds the target protein with high affinity that is fused via a linker to the transmembrane and cytoplasmic domains of different phagocytic receptors (FCERG1, MRC1, MERTK, CLEC4L). Notably, for each target protein, staff have identified two or more CPRs (based on the different phagocytic receptor fusion) that selectively bind to the target protein and mediate rapid internalization of the targeted protein. In the central nervous system (CNS) both microglial cells and astrocytes can be phagocytic. The team is able to selectively transduce astrocytes in neonatal and adult mice using appropriate rAAV vectors. Microglia cells remain difficult to transduce with high efficiency *in vivo*, but with novel rAAV vectors we can transduce them efficiently ex vivo. These engineered microglial can then be studied ex vivo in relevant models or transplanted into the brains of mice. Using select *in vivo* and ex vivo models of Aβ and tau pathology, including our novel brain slice culture models of tauopathy, staff will evaluate the ability of CPRs to have disease modifying effects when delivered before pathology develops or when pathology is already robust. If successful, like CAR-Ts, it is likely that appropriately targeted CPRs may have applicability to AD and many other 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.

7. **Grant #:** 21A08 Epitranscriptomics in Models of Alzheimer's Disease

Principal Investigator: Karen N McFarland, PhD

Organization: University of Florida

Abstract: At the pathological and molecular level, hallmarks of Alzheimer's disease (AD) include the accumulation of beta-amyloid (Aβ) protein into amyloid plaques and Tau protein into neurofibrillary tangles. Given these features, AD falls into the broad category of proteinopathies which describes the abnormal production and accumulation of proteins and indicates that this process plays a key role in the disease mechanism. These accumulations of Aβ plaques and neurofibrillary tangles and all the associated proteins within them are neurotoxic and lead to cell dysfunction and death.

The epitranscriptome describes the dynamic and reversible modification of methyl groups to nucleosides of RNA transcripts. Changes in the epitranscriptome are thought to allow for rapid alterations of protein levels in response to environmental cues and adds an additional layer of control for protein levels. N6-methylation at adenosine residues (m6A) are present in up to one-half of all mRNA transcripts in the mammalian brain. Methyl groups are added by methyltransferases ("writers") and removed by demethyltransferases ("erasers"). Research staff found that levels of these enzymes are altered in primary microglial cells after treatment with fibrillar and oligomeric forms of Aβ. However, whether m6A levels are altered in this and other models of AD and in AD patient brains is an unanswered question.

Mouse microglial cultures were treated with monomeric, oligomeric, or fibrillar forms of Aβ for one or 12 hours. Previous published work from the lab has described that these treatments result in changes in transcript levels not only compared with control conditions but also between various forms of Aβ. Following the harvest of the cell cultures, RNA was extracted and followed by a quality assessment. For Specific Aim 2, RNA was acquired from longitudinal timepoints from the TgCRND8 mouse model - a model of Alzheimer's disease that progressively accumulates Aβ in the brain. Given the low yields of RNA from the microglial cultures, the alternative approach described in the project proposal - long-read sequencing technology using the MinION flowcell from Oxford Nanopore Technologies - was tested on RNA ranges at the levels obtained in the experiments described. These initial experiments indicate that at lower input levels utilizing the long-read MinION flow-cells to sequence low-input RNA samples is feasible. Additionally, the amount of information that can be attained is rich even at the lowest level of input RNA tested, as assessed by the visualization of differences in transcript splice isoforms. Next steps for this project will utilize the MinION flow cells to sequence these Aβ-treated microglial samples as well as the longitudinal samples from the amyloid transgenic mouse line, TgCRND8 and assess the results for changes in the levels of m6A residues.

While this project is in its beginning stages, results from these experiments should shed a new light on our understanding of how neurotoxic proteins are aberrantly produced in AD. This new line of investigation may also open epitranscriptomics as an innovative avenue of investigation into other neurodegenerative disorders as many of these diseases are also categorized as proteinopathies.

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 #:** 21A09 Go Your Own Way: Evaluating Neurofeedback-Induced Plasticity to Improve Spatial Navigation Behavior in Older Adults at Risk for Alzheimer's Disease

Principal Investigator: Steven M. Weisberg, PhD

Organization: University of Florida

Abstract: Spatial navigation is an essential task, without which even finding the kitchen from the bedroom becomes a challenge. With decreased ability to navigate comes decreased safety and an overall decline of independence and quality of life. Losing the ability to navigate is common in normal aging and is exacerbated in Alzheimer's disease (AD). This loss of spatial navigation function in healthy and pathological aging has primarily been linked to decreased functional integrity of the hippocampus – a brain region supporting flexible navigation behavior. Yet, previous research on this deficit discounts alternative navigation strategies, supported by the caudate nucleus, which remain intact among older adults. The goal is to assess and attenuate age-related decline of navigation success (whether a navigator reaches their goal) by dissociating success from navigation strategy (the cues and cognitive processes a navigator employs to encode the environment). Multiple approaches combine behavioral, neural, and genotypic assessment with a novel real-time neurofeedback intervention. Research staff propose three specific aims: to determine the behavioral and neural correlates of spatial navigation strategies in healthy older adults and older adults who are at risk for developing AD, i.e., diagnosed with amnestic mild cognitive impairment (aMCI); to evaluate the efficacy of a real-time functional magnetic resonance imaging (rtfMRI) guided neurofeedback training to increase hippocampal or caudate activation, thereby improving navigation success; todetermine whether carriers of a genetic marker, apolipoprotein E4 (ApoE4), which predisposes carriers to develop AD, are more likely to show navigation deficits or may be more (or less) amenable to rtfMRI interventions. In particular, the researchers hypothesize a shift from a hippocampal-based navigation strategy in younger adults to a caudate-based strategy in older adults, with no age-related change in navigation success. Further, the researchers hypothesize that this neural shift and associated behavioral effects are more pronounced in individuals at elevated risk for developing AD (i.e., ApoE4 allele carriers) and in aMCI. Results from this proposal have tremendous potential to inform basic scientific understanding of neural and genetic markers for behavioral deficits in spatial navigation in healthy and pathological aging and can directly inform public health intervention. Linking neural activity in the hippocampus and caudate to behavioral changes in spatial navigation allows us to specify which aspects of navigation behavior are preserved and which are impaired in aging and age-related disease. These data have direct translational impact by developing an improved mechanistic understanding of the link between neural processes, genetics, and human behavior allows for more precise determination for who may need clinical support before they get lost or wander.

Since the award was activated on 05/02/2021, the University of Florida worked to meet the background screening requirement for the three named personnel on the grant. The project is Institutional Review Board approval for recruitment and scientific methods and a preregistration for the planned fMRI project was submitted. Research staff began recruiting and prescreening younger and older adults. fMRI data processing pipeline developed, and tested Staff and personnel are trained. Genetic assay analysis protocols for both in-lab protocols (sample collection) and out-of-lab processing.

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 #:** 21A10 Impact of Severe Systemic Infections on Brain Pathology and Local Immune Response

Principal Investigator: Stefan, Prokop, MD

Organization: University of Florida

Abstract: Alzheimer's disease (AD) is the most common cause of dementia, currently affecting more than 580,000 Floridians. It is known that severe systemic infections can trigger cognitive decline and the current COVID-19 pandemic has brought a surge of severe viral illness highlighting the importance of understanding the short- and long-term impact of acute infections on cognition and precipitation of neurodegenerative disease in survivors.

In this context, the overarching goal of this proposal is to recruit Floridians who have survived COVID-19 infections into the brain donation program of the University of Florida Neuromedicine Human brain and tissue bank (UF HBTB) to allow for a detailed neuropathological workup, as well as an in-depth analysis of local immune responses in the brains of these patients. During the first six months of funding research staff have undertaken outreach efforts, including personal communications with interested participants, distribution of flyers and launch of a webpage. These efforts have been extremely successful, allowing us to recruit a total of nine COVID-19 survivors into the brain donation program. Eight of these participants subsequently died and staff was able to procure their brains for the UF HBTB.

A Neuropathological workup has been completed on the majority of these brains, revealing a variety of neuropathological changes, including but not limited to AD neuropathological changes, Lewy body pathology, as well as cerebrovascular disease. As a next step, staff will analyze the local immune response in these brains and compare the findings with existing data sets of patients who suffered from neurodegenerative diseases but did not have a COVID-19 infection.

Our recruitment efforts in the first six months of funding have been very successful and the team is confident to continue on this trajectory to allow for a comprehensive assessment of the impact of COVID-19 infections on the burden of neurodegenerative disease in Florida. In addition to the immediate results of our autopsy studies, this project will also be able to create a registry of patients signing up for brain donation, to provide a longitudinal view of the emergence of neurodegenerative disease in the state of Florida in the upcoming years following the conclusion of the COVID-19 pandemic.

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 #:** 21A11 Effects of Cannabis on Alzheimer's Disease-Related Pathology and Cognitive Decline

Principal Investigator: Barry Setlow, PhD

Organization: University of Florida

Abstract: Adults over age 65 represent the fastest growing group of cannabis users, but they are also at the greatest risk for Alzheimer's disease (AD) and age-related cognitive decline. This project uses rodent models to determine how chronic exposure to cannabis and cannabinoids affects AD pathology (Aim 1) and age-related cognitive impairments (Aim 2). Under Aim 1, experiments are determining the pharmacokinetics of delta-9 tetrahydrocannabinol (THC, the primary psychoactive component of cannabis) in mice exposed to cannabis smoke. These data will be used to determine the optimal parameters of cannabis smoke exposure in mice expressing AD pathology. Under Aim 2, initial data suggest that in aged rats, daily oral consumption of THC enhances working memory (the ability to keep information "in mind" for short periods of time). In this experiment, young adult and aged rats were trained in a working memory task. Rats were then divided into two groups and allowed to eat either plain gelatin or gelatin containing THC daily, while they continued testing in the working memory task. As in humans, aged rats had worse working memory than young adult rats at baseline. After chronic THC, however, aged rats performed comparably to young adults (and better than aged rats that ate plain gelatin). Interesting, young adults that ate THC performed worse than young adults that ate plain gelatin, indicating that THC consumption has opposite effects in young adult and aged rats (i.e., it improves working memory in aged rats but impairs working memory in young adult rats). Ongoing studies are in the process of repeating this experiment in additional cohorts of rats.

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

Collaborations: All components of the project are conducted at University of Florida, in the Colleges of Medicine and Pharmacy. In addition to Dr. Barry Setlow (PI, Dept. of Psychiatry), the project involves collaborators Drs. Jennifer Bizon and Jada Lewis (Dept. of Neuroscience), and collaborators Drs. Christopher McCurdy (Dept. of Medicinal Chemistry) and Abhisheak Sharma (Dept. of Pharmaceutics). The project additionally involves the work of three graduate students (Sabrina Zequeira and Emely Gazarov, College of Medicine, and Erin Berthold, College of Pharmacy).

Journals: None at the time of reporting.

Patents: None at the time of reporting.

11. **Grant #:** 21A12 Role of Irisin as Mediator of Exercise-Related Cognitive Improvement in Alzheimer's Disease

Principal Investigator: Karina Alviña, PhD

Organization: University of Florida

Abstract: For the first aim of the project, research staff will be using postmortem samples from human patients from the University of Florida Brain Bank. Staff has started compiling the project's sample database to be provided by Dr. Stefan Prokop. At the same time, staff has evaluated different antibodies using mouse brain and muscle tissue to find the most effective one and use it to stain human brain samples as proposed. Two different sources have been used for the antibody, and researchers are troubleshooting to get the best staining results.

The second aim will be using a mouse model of Alzheimer's disease (mouse strain CRND8). For these experiments, staff started the breeding colony that will produce mice for the planned experiments. A good number of mice are ready to start with electrophysiology and behavioral experiments in the next couple of months.

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 #:** 21A13 The Importance of the Innate Immune Response as a Mechanistic Link between Traumatic Brain Injury and Alzheimer's Disease

Principal Investigator: W. Dalton Dietrich, PhD

Organization: University of Miami

Abstract: Traumatic brain injury (TBI) is a significant risk factor for the development of Alzheimer 's disease (AD) and AD related dementias. Although this interrelationship represents an important heath problem to the citizens of Florida especially due to the high incidence of TBI and a growing aging population, the causative relationships between these two conditions is not known. In mouse models that incorporate genetic risk factors for AD, time-based patterns of emerging cognitive dysfunction have been described with evidence for TBI accelerating the emergence and severity of AD-like pathologies. The role of inflammation and the abnormal activation of the innate immune response through intracellular sensory complexes that detect cell damage and metabolic disturbances (inflammasome) in the pathogenesis of TBI and AD has been emphasized. An important consequence of inflammasome activation is the release of large protein complexes termed specks which contribute to local as well as remote organ system damage. A major goal of this study is to determine the mechanisms whereby TBI-induced inflammasome signaling contributes to the progressive patterns of genetic risk factors in AD, thereby targeting mechanistic links between the pathogenesis of TBI and AD. Our central hypothesis is that inflammasome-mediated innate immunity in AD augments TBI-induced inflammation and contributes to memory impairments in models of AD. Research staff also propose that small particles termed extracellular vesicles (EVs) and inflammasome specks play a central role in the innate immune signaling by translocating inflammasome proteins to neighboring cells after TBI, thus causing protein aggregation, neurodegeneration and progressive cognitive decline. Moreover, the neutralization of secreted components of the inflammasome complex with an antibody against the inflammasome will decrease inflammasome signaling after TBI and reduce inflammasome-dependent cell death resulting in improved behavioral outcomes. To test this hypothesis, three specific aims are proposed. The

first aim will determine the temporal activation and cellular distribution of TBI-induced inflammasome activation on AD pathology. Staff hypothesize that TBI produced in an AD-transgenic model augments deleterious inflammatory processes, cognitive decline and neuropathology compared to non-injured mice. The second aim will establish the effect of TBI on inflammasome activation and severity of cognitive deficits in AD mice. The team hypothesize that inflammatory derived EVs containing inflammasome proteins obtained from AD mice primed by TBI and systemically infused into non-injured AD-mice will aggravate inflammasome activation, cognitive performance and histopathological outcomes. Aim three will test the therapeutic effects of inflammasome inhibition and speck accumulation on histopathological and behavioral outcomes after TBI in control and AD-transgenic mice. Staff hypothesize that therapeutic strategies that inhibit inflammasome activation after TBI in AD-mice will improve outcomes as compared to vesicle-treated TBI animals. Together these studies will help identify novel therapeutic targets and treatment strategies for ameliorating the deleterious effects of TBI and AD on learning and memory.

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.

13. **Grant #:** 21A14 Cyclic Nucleotide Regulation in Alzheimer's Disease and Brain Trauma

Principal Investigator: Coleen M. Atkins, PhD

Organization: University of Miami

Abstract: This project studies Alzheimer's disease (AD) and the interaction with traumatic brain injury (TBI). In Florida, there are 580,000 people aged 65 and older with AD. TBI is a significant public health problem in Florida as well and in 2018, there were 20,891 non-fatal hospitalizations in Florida for TBI. Many Floridians do not fully recover after a TBI and there are approximately 370,000 Floridians living with long-term disabilities resulting from TBI. Adults ages 55+ have the highest rate of TBI incidence. The combined prevalence of AD and TBI indicate that TBI occurring in the context of developing AD is a significant clinical problem for Florida. This proposal will develop a therapeutic to be given to this patient population after a TBI, before or during the development of AD to slow the progression of cognitive symptoms and treat the underlying pathology of synaptic loss. The treatment that this study tests is a selective inhibitor of phosphodiesterase 4B, T2409. During this progress period, mice that are genetically altered to develop AD received a surgery to induce TBI and were compared to non-injured mice. The mice were treated with the drug T2409 to see if this drug treatment would improve learning and memory after TBI. When the mice were tested in young adulthood before the onset of AD, the AD mice had normal learning and memory ability as compared to wild type, normal mice. The next step in this project is to test whether aged AD mice that are in the early stage of AD will develop learning and memory deficits after TBI. The results from this project will provide knowledge on when an intervention should be initiated in TBI patients to prevent the development of learning and memory deficits associated with AD. This study has the potential to

impact the health of Floridians by improving their cognitive functioning and slowing the underlying AD-associated pathology after a TBI.

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

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

14. **Grant #:** 21A15 Contributions of Menopause-Induced Epigenetic Mechanisms on Alzheimer's Disease Pathogenesis

Principal Investigator: Claes Wahlestedt, MD, PhD

Organization: University of Miami

Abstract: There is limited understanding of the mechanisms that underlie the sexual dimorphism seen in Alzheimer's disease (AD). The proposed studies will help identify epigenetic mediators linking female sex and aging to AD. This study will highlight the need for future drug trials to stratify patients based on sex, and perhaps the need to study efficacy in single sex cohorts. The long-term goal of this research is to better inform future AD therapies.

Women are nearly twice as likely to develop AD compared to men and experience more rapid cognitive decline and worse pathology, for reasons that remain unknown. Furthermore, sex differences both clinically and pre-clinically are often overlooked and underreported, making it difficult to determine how much sex differences influence AD. One hypothesis for the higher prevalence of AD in women lies in the drastic changes in sex hormones women experience as they traverse menopause, resulting in a depletion of estrogen and progesterone in post-menopause. Menopause has been reported to cause changes in epigenetic modifications, including histone acetylation. The lab has shown previously that regulation of epigenetic modulators through histone deacetylase (HDAC) inhibition improves memory in murine models of AD, while normalizing AD-related genes. Human imaging studies have uncovered that increased levels of Aβ begins in peri-menopause, even in cognitively normal women, when compared to men of the same age or pre-menopausal women. A decline in glucose metabolism and mitochondrial efficiency, factors that have both been implicated in AD, in the brains of women is also seen to commence in peri-menopause. To study the relationship between sex, mitochondrial health, and staff propose to utilize a murine model of AD. To date, no rodent studies have studied epigenetic modifications in the brain during the peri-menopausal state. Preliminary data from our lab suggests that sexual dimorphism is observed in cognition and glucose metabolism in an aged AD mouse model, suggesting animal models can be used to study these sex differences. Studying epigenetic changes that are occurring in the brain during the unique neuroendocrine state of peri-menopause might be key to understanding AD onset in women. Therefore, staff propose to uncover the acetylation and gene expression changes occurring in the brain in peri- and post-menopause-like states in a murine model, with the long-term goal of being able to develop more personalized or sex-specific treatments to AD. This is a newly awarded grant, executed in June 2021. The research staff has started buying reagents and conducting experiments on relevant animals. Impact to Floridians: Florida has the second highest population of individuals living with AD in the U.S. and is projected to increase nearly 30% over the next five years. Data suggest that early detection may help delay AD symptoms,

but early biomarkers are lacking. Through the work proposed here, the role of menopause-mediated changes occurring in the brain during the transition from peri-menopause to post-menopause transition could be key to understanding AD onset in women and may improve early AD detection in Florida and beyond.

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 #:** 21A16 Detectin and Reduction of Scams Susceptibility Among Hispanic/Latin and Non-Hispanic/Latin Individuals with Mild Cognitive Impairment and Alzheimer's Disease

Principal Investigator: Bonnie E. Levin, PhD

Organization: University of Miami

Abstract: Research staff have continued to meet every other week over Zoom to improve the study design and methods. The Scam Awareness Questionnaire was adapted for English and Spanish speaking individuals with cognitive limitations, after realizing that the phrasing on the originally proposed questionnaires was too complex. The team also created a Demographic intake questionnaire, with questions addressing overall physical and cognitive health, functional activities of daily living, living arrangement, details on computer usage, prior scam victim history, and financial literacy. Staff have revised the Caregiver and Participant pre-intervention and post intervention questionnaires, adapted from newly published literature on scamming and scamming awareness. During the second quarter, the team also revised the intervention protocol, to include a pre-intervention visit, for many individuals, it was too much information presented in each session. To address this issue, the team developed an introductory presentation (pre-intervention) in which scamming is defined and basic terms are introduced (exploitation, scoundrel) with concrete examples for the participant and caregiver to view and then discuss before the actual intervention takes place. The precautions regarding pandemic protocol are still in place, which continues to hamper recruitment. Nevertheless, staff are still actively engaged in telehealth and virtual assessments and remain confident that recruitment of participants will be successful, even virtually if needed.

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

Collaborations: Marlene Cabrera, a second year postdoctoral fellow in the Division of Neuropsychology and Cognitive Neuroscience, continues to meet with our team to assist in translation issues and scamming protocol.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

16. **Grant #:** 21A17 The Role of ABCA7 in Alzheimer's Disease in African Americans

Principal Investigator: Holly N. Cukier, PhD

Organization: University of Miami

Abstract: During the first five months of the grant, the research staff ensured all proper certification was in place. The grant was approved for Recombinant DNA and Gene Transfer technology to be performed by the Institutional Biosafety Committee (IBC #21-079). Once this was established, the researchers began ordering the supplies necessary to begin this study and planning out the first experiments. The staff already established induced pluripotent stem cell (iPSC) lines to perform this project were transferred from being grown on mouse embryonic fibroblasts (MEFs) with the mTeSR1 medium (STEMCELL Technologies) to the feeder free matrix vitronectin with the StemFlex medium (ThermoFisher Scientific).

This change in methodology will allow for easier growing and passaging of the iPSCs, as well as a smoother transition when generating microglia cells from the iPSCs. Two patient-derived African American iPSC lines with 44 base pair ABCA7 deletions were successfully transitioned to grow on vitronectin in StemFlex (AD392081 and AD387780). In addition, staff also obtained one line from the University of California, Irvine Alzheimer's Disease Resource Center (ADRC) iPSC Core, iPS80 clone #4 generated from fibroblasts from a 77 year old, neurologically normal woman [mini-mental state exam (MSSE) = 30]. The cells were initially growing on GFR Matrigel in TeSR E8 media, and were successfully transitioned the line to grow on vitronectin in StemFlex media for consistency across lines. Furthermore, this new African American control line was Sanger sequenced to ensure that it did not have the 44 base pair deletion in ABCA7, which is present in ~10% of aged control individuals. The deletion does not occur in iPS80, and it is therefore an appropriate control for this proposal.

Unfortunately, a few setbacks have occurred. In addition, supply chain shortages, probably connected to the COVID-19 pandemic, some reagents and supplies on backorder and sometimes replacements or work arounds had to be arranged. For example, the StemFlex Medium (ThermoFisher Scientific) has been on backorder for months. Staff replaced this with StemScale PSC Suspension Medium (ThermoFisher Scientific), which works well for growing iPSCs, but may lead to variability between experiments in the future. Additionally, for the microglia protocol, STEMCELL Technologies is currently backordered for the STEMdiff Microglia Maturation kit through November. Therefore, the team planned to modify the protocol back to the academic study from which this kit was derived, as described from the Blurton-Jones lab in McQuade, et al, 2018. Furthermore, the protocol calls for the cells to be plated on Matrigel (Corning), which the team has attempted to replace with vitronectin (ThermoFisher Scientitific). Initial attempts at differentiating one of the ABCA7 patient iPSC lines (AD387780) and the control iPS80 line into both microglia and forebrain organoids have not yet been successful, potentially due to the modifications of medium and protocols, but staff are in the process of troubleshooting these issues.

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 #:** 21A18 Functional Analysis of UNC13B Gene Polymorphism in a Hispanic Population with Alzheimer Disease.

Principal Investigator: Katrina Celis Delgado, MD

Organization: University of Miami

Abstract: Differentiation of the remaining three induced pluripotent stem cell (iPSC) lines was continued into Neural Progenitor Cells (NPCs) using the STEMdiff kit from STEMCell Technologies. This was accomplished by growing single celled iPSCs in AggreWell plates for five days to form neural aggregates. These are then replated on poly-L-ornithine/L-aminin coated plates, where they formed neural rosettes. They will be grown further into NPC and then young cortical neurons for functional characterization. In total, staff have generated NPC from five individuals bearing the UNC13B Asp238Glu variant and two individuals without the variant from the family being studied. In addition, the necessary supplies for the neuronal differentiation have been purchased, including the STEMdiff Forebrain Neuron Differentiation kit and Neuronal Maturation kit. In addition, two additional iPSC lines from two individuals without the UNC13B Asp238Glu variant that are unrelated to the family baring studied are also being differentiated into NPC to be used as controls for the functional analysis.

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 #:** 21A19 Postdoctoral Fellowship in Cross-Cultural Neuropsychology and Cognitive Neuroscience

Principal Investigator: Rosie Curiel Cid, PsyD

Organization: University of Miami

Abstract: The Principal Investigator posted the position to obtain the most qualified candidates who would be interested in developing a career within the field of Alzheimer's Disease and Alzheimer's Disease Related Dementia (ADRD). It was decided to offer the fellowship position to Diana Hincapie, Psy.D. who is a graduate from Nova Southeastern University with a doctoral degree in Clinical Psychology and major in Neuropsychology. The decision was supported by Dr. Hincapie's academic achievement history, prior training experiences, research goals, and recommendations from previous supervisors. On 08/02/21, upon completing all institutional requirements and the University of Miami orientation, Dr. Hincapie began her formal fellowship training at the Center for Cognitive Neuroscience and Aging, Psychiatry Department, University of Miami Miller School of Medicine. Since her commencement, Dr. Hincapie has been receiving extensive orientation and training related to the administration, scoring, and interpretation of traditional neuropsychological assessments methods used for the detection and diagnosis of AD+ADRD, becoming familiarized with our clinical research protocols, and the operational aspects of active research studies (e.g. recruitment methods, data entry system, protocol implementation, institutional trainings, etc.). So far, she has been acclimating very well to the

clinical research fellowship. Dr. Hincapie is attending weekly consensus conferences with a multidisciplinary team and has begun the neuroscience didactic series.

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.

19. **Grant #:** 21A20 Carotid Ultrasound Imaging Markers of AGINg and Endothelial function in Risk of Alzheimer's Disease: The Florida IMAGINE Study of AD Risk

Principal Investigator: Tatjana Rundek, MD PhD

Organization: University of Miami

Abstract: Research staff will perform a high-resolution carotid ultrasound imaging in the participants enrolled to the 1FL ADRC. Novel carotid IMAGINE measures of arterial wall structure include intima-media thickness (IMT), presence and characterization of plaque (area, Gray Scale Median echodensity), geometry (common-to-internal carotid angle), and assessment of endothelial function (stiffness, blood flow velocity-BFV). The team hypothesizes that carotid IMAGINE measures are prevalent, with over 50% of participants having plaque or other measures above the median (or BFV below the median). They are more prevalent in Hispanic-Latino (HL) participants. We will additionally correlate the IMAGINE measures with magnetic resonance imaging (MRI) markers of CSVD (white matter hyperintensity volume-WMHV, silent brain infarcts-SBI, microbleeds-CMB, and enlarged perivascular spaces-ePVS), neurodegeneration, and amyloid load. Staff hypothesize that carotid IMAGINE measures are associated with greater burden of CSVD (WMHV above the median or any presence of SBI, CMB, ePVS), total cortical volume in Alzheimer's disease regions, and presence of amyloid. These associations are more pronounced in HL participants and modified by APOE*ε4 status.

Finally, the team will determine the effects of IMAGINE markers on both novel as well as standard neuropsychological measures tapping different cognitive domains (failure to recover from semantic interference, attention, global memory impairment, executive function, language, visuospatial skills/praxis). Staff hypothesize that carotid IMAGINE measures are associated with cognitive performance. These associations are more pronounced in HL participants; mediated by the burden of CSVD, neurodegeneration and amyloid load; and modified by APOE*ε4 status.

The IMAGINE project received IRB approval. A flyer and script for the study team to use to recruit participants was developed. These new materials were submitted to the IRB and approved. The IRB also approved a protocol modification to include payments to study participants, which will provide additional incentive and potentially increase our recruitment success. Two study subjects have completed enrollment.

The carotid ultrasound scanning protocol is in place. It will be performed at two locations, the main Medical Campus of University of Miami Miller School of Medicine, and the University of Miami Coral Gables Campus in the Research MRI facility of the Department of Psychology. This decision was made to accommodate participants at both locations, reduce participant burden and minimize travel time for participants. In order to establish the carotid ultrasound imaging

protocol at the Research MRI facility all personnel completed an MRI safety training, took a certification test and received certification in medical safety of MRI. This was needed due to proximity of the room with ultrasound imaging to a powerful magnet and potential damage from the effects of ferromagnetism. An in-service training on the carotid ultrasound procedure took place for the research team, so they could describe the non-invasive procedure during recruitment. The PhD student at the University of Miami School of Biomedical Engineering (BME) Taylor Ariko, was trained in carotid ultrasound imaging and can now also perform the carotid ultrasound along with the study coordinator Digna Cabral, under the supervision of Dr. Rundek (PI).

Several planning meetings took place with the members of the UM Center for Cognitive Neuroscience and Aging (CNSA) which includes the UM 1FL ADRC leaders, David Loewenstein, PhD, (lead of UM Clinical Core and Co-Director of 1FL ADRC) and Rosie Curiel, PhD, (lead of 1FL ADRC Recruitment Core). The CNSA clinical team will assure the recruitment of the participants in the study, obtain clinical and MRI/PET data and provide access to other 1FL ADRC data (e.g., APOE*ε4 genotype) for the purpose of this study. The CNSA team will also provide neurocognitive expertise as recognized leaders in cognitive assessments for populations at AD risk. The study team has established regular bi-weekly research and operational meetings to discuss study recruitment and any issues related to recruitment, monitor ongoing protocol safety measures, ensure quality of the data collection including carotid ultrasound, and ensure the quality of the post-processing and analyses of the MRI scans.

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

Collaborations: We have established a strong collaboration across University of Miami, including the University of Miami Center for Cognitive Neuroscience and Aging (CNSA) led by Dr. David Loewenstein (CNSA Director) and Dr. Rosie Curiel (CNSA Co-Director), and their research teams.

We have also established a collaboration with the Department of Radiology (Dr. Mohammed Goryawala, a study physicist) and the University of Miami School of Biomedical Engineering (BME) and the BME PhD Program (Taylor Ariko, PhD Student), who is now trained on the study protocol and has been assisting with procedures.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

Patents: None at the time of report.

20. **Grant #:** 21A21 Regulation of Proteostasis by Sleep in Alzheimer's disease

Principal Investigator: Grace Zhai, PhD

Organization: University of Miami

Abstract: Sleep disturbance and aberrant sleep patterns are commonly observed in patients with Alzheimer's disease (AD). Growing evidence suggests that in addition to being a symptom, sleep disturbances can also drive the progression of neurodegeneration. Neurodegeneration in AD patients is marked by the formation of protein aggregates in the brain. The complex interplay between sleep and protein homeostasis remains largely uncharacterized in part due to the

limitations of the animal models that could allow simultaneous sleep behavior monitoring/manipulation and cellular and biochemical analysis *in vivo*.

Research staff propose an integrated approach to characterize the molecular interplay between sleep regulation and neurodegeneration *in vivo* in Drosophila. The main goal of this project is to investigate the cellular and molecular mechanisms by which sleep regulates protein misfolding, aggregation, and clearance in Drosophila models of AD. The proposed research is built on our preliminary data showing the impact of sleep disruption on protein aggregation. This study will integrate high resolution immunofluorescent and electro microscopic imaging, comprehensive biochemical assays, sleep monitoring and analysis, and neuronal functional recordings to answer the following key questions: how sleep disruption affects protein aggregation and clearance, whether a disrupted sleep pattern changes the amyloid-like biochemical properties of protein aggregates, and how disrupted sleep homeostasis alter neuronal cellular changes, including mitochondrial dynamics and function, microtubule-based axonal trafficking, and synaptic integrity. The project will reveal the cellular mechanisms that connect sleep disruption to proteotoxicity and in so doing, will form the basis for innovative neuroprotective strategies that may halt or reverse AD progression.

This proposed collaborative project will address for the first time, how sleep regulates protein homeostasis in neurodegeneration. The proposed work will potentially lead to the design of novel disease-modifying therapies based on targeting sleep dysregulation, which would have far-reaching implications for alleviating neurodegenerative diseases and improving the quality of life of patients suffering from AD.

This is a newly started grant (start date 5/5/2021). In the past five months, the team has successfully gathered experimental tools and reagents. Specifically, the team has, established the sleep monitoring system for AD model flies; set up the experimental protocols for sleep modulation paradigms, which include the sleep disruption and sleep induction; and set up genetic crosses to obtain AD model flies that would subject to sleep modulation. The project has successfully started on schedule and staff expect on time delivery of the results.

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

Collaborations: This is a multi-disciplinary collaborative project between Dr. Grace Zhai, PhD in Department of Molecular and Cellular Pharmacology in Miller School of Medicine and Dr. Sheyum Syed, PhD in Department of Physics in University of Miami. Given that Dr. Zhai's research lab is located in the medical campus and Dr. Syed's lab is on the Coral Gables undergraduate campus, this project provides training opportunities to both undergraduate, graduate and medical students to collaborate on addressing the issue of Alzheimer's Disease.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

21. **Grant #:** 21A22 Postdoctoral Fellowship in Neuropsychology and Cognitive Neuroscience

Principal Investigator: David Loewenstein, PhD

Organization: University of Miami

Abstract: Alexandra Ortega, Psy.D. was the most competitive candidate in the pool of applicants to the fellowship program. Staff posted the position nationally and interviewed several candidates who were interested in completing the postdoctoral fellowship in neuropsychology and cognitive neurosciences. with an emphasis on neurodegenerative diseases/geriatric neuropsychology. Dr. Ortega is a bilingual and bicultural clinical psychology graduate who majored in neuropsychology. Dr. Ortega has an excellent academic achievement history, prior training experiences, future research interests within the field of aging and cognition, endorsements from previous supervisors, and commenced formal training at the Center for Cognitive Neuroscience and Aging, Psychiatry Department, University of Miami Miller School of Medicine on 08/02/2021. She has been onboarding and received extensive training in the administration, scoring, and interpretation of traditional neuropsychological assessments methods used for the detection and diagnosis of Alzheimer's Diesase and Related Dementia, NIH/NIA research protocols, and is now familiarized with the CNSA research operations (e.g. recruitment methods, data entry system, protocol implementation, institutional trainings, etc.). She is attending weekly consensus conferences with a multidisciplinary team and has begun the neuroscience didactic series. Dr. Ortega has been engaging in weekly supervision and has been adjusting very well to her new position.

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.

22. **Grant #:** 21A23 Effects of Novel Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonists on Comorbities in Alzheimer's Disease with Diabetes Mellitus

Principal Investigator: Mark S. Kindy, PhD

Organization: University of South Florida

Abstract: The proposal was executed on 06/11/2021. As part of this project, research staff have begun generating enough of the P5 and Fc-P5 for the studies. This entails screening more compounds that might have beneficial effects. Testing the compounds *in vitro* (primary neuronal cultures) is currently underway to determine the impact of the agonists on neuronal survival and outcomes. Staff are also, preparing the animals for the *in vivo* studies.

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

Collaborations: The current award is a collaborative effort between Dr. Mark Kindy, Professor and Director in the Department of Pharmaceutical Sciences, College of Pharmacy, University of South Florida (and Senior Research Career Scientist James A. Haley VAMC) and Dr. Patsy McDonald, Associate Member, Dept. Cancer Physiology; Moffitt Cancer Center.

Journals: None at the time of reporting.

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

23. **Grant #:** 21A24 Exploiting Molecular Chaperones to Understand the Impact of Tau Aggregation on Prion-Like Spreading in Alzheimer's Disease

Principal Investigator: Laura J. Blair, PhD

Organization: University of South Florida

Abstract: This project has had steady progress in the just over one quarter it has been funded. The main goals are to identify molecular chaperones that alter tau seeding and release, which is implicated in Alzheimer's disease (AD) pathogenesis. During this reporting period, the research team organized and confirmed the sequences of the molecular chaperone plasmids that are used to express discrete molecular chaperones in cells, which will be used for screening. This involved generating and isolating additional Deoxyribonucleic acid (DNA) material and sequencing of this material, which is now fully validated. This is an important preparation step to prepare for the upcoming assays and unsure the data generated can be properly interpreted.

Recombinant tau protein was produced and purified, and tau seeds were generated by aggregating this tau protein. This final product (tau seeds) is used for the cell culture experiments in Tau RD P301S HEK293T FRET biosensor cells. The production of tau protein and aggregation is an ongoing activity to support the ongoing assays for this project. Tau RD P301S HEK293T FRET biosensor cells were treated with P301L tau seeds at various concentrations compared to control treated cells, as planned in the proposal. These data revealed that that highest concentration (1 µM) is very toxic and that the lower concentrations (10, 30, 100 nM) have higher variability across replicates. The 300 nM tau P301L tau concentration was found to be consistent across replicates and to have overall fair health of the cells. To further improve the health of the cells in this assay, the timing of the treatments was tested as well as the cell growth conditions. The data from replicates of these assays revealed a streamlined workflow with improved health of the cells, which enables the planned screen of curated library of molecular chaperones in this assay to be initiated next quarter.

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 #:** 21A25 Project Title: Building Dementia Care Network and Community Capacity for Older Asian Immigrants with Limited English Proficiency in Florida

Principal Investigator: Nan S. Park, PhD

Organization: University of South Florida

Abstract: Approximately 5.8 million Americans have been affected by Alzheimer's disease and other related dementia (ADRD), and the numbers are estimated to increase to nearly 14 million cases by 2050 (Alzheimer's Association 2020; Brookmeyer, Abdalla, Kawas, & Corrada, 2018). Florida has a large number of ADRD cases, 580,000 in 2020, and the numbers are expected to increase to 720,000 by 2025 (Alzheimer's Association, 2020). One group that is particularly vulnerable is older immigrants with Limited English Proficiency (LEP). With linguistic and cultural

barriers and unfamiliarity with the mainstream health care system, older immigrants tend to be uninformed about ADRD and related services (Mukadam, Cooper, & Livingston, 2013). Adding to the problem, Asian Americans are an extremely diverse group including more than a dozen ethnic groups and 300 languages, and more than half of older Asian Americans have LEP (Lopez, Ruiz, & Patten, 2017; Pandya, McHugh, & Batalova, 2011). The number of Asian Americans in Florida increased by more than 70% from 2000 to 2010 (Rayer, 2014).

Many older Asian Americans are foreign born and they are prone to cultural stigma and misconceptions about ADRD (Casado, Hong, & Lee, 2018; Hermann et al., 2018). These barriers are likely to deter early diagnosis and treatments that can benefit those with the disease and provide guidance for caregivers (Alzheimer's Association, 2020; Cooper, Tandy, Balamurali, & Livingston, 2010; Mukadam, Cooper, & Livingston, 2013). Another barrier is the disruption in the socio-environmental context posed by the actual immigration experience. Social networks built in their native country are likely to be fragmented or lost, a process that has been referred to as the "broken convoy" effect (Park et al., 2015). Moreover, the social opportunities and resources in the host country may differ substantially from those in their native country. Considering that knowledge about the disease and related health services is critical for actual use of services, the present study will promote the knowledge and service utilization of the three largest groups of older Asian Americans with LEP in west Florida: Chinese, Korean, and Vietnamese.

Based on the dementia care network (DCN) conceptualization (Kally, Cherry, Howland, & Villarruel, 2014), the project has three research objectives: To conduct needs assessment for older Asian Americans and assess the community resources and barriers to deliver ADRD services. In part, older Asian Americans will participate in a survey to assess their knowledge and awareness of both ADRD and access to ADRD-related services. To build community capacity for dementia care by establishing ADRF care network with community leaders and older Asian Americans and their families. To establish web-based resources for ADRD and relevant services and disseminate the resources. Taken together, the goal of the project is to build community capacity for early detection of ADRD and utilization of services by promoting education of older Asian Americans and their families and ethnic community leaders on ADRD knowledge and related services.

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.

Fiscal Year 2020-2021 Active Grants

(Funding Year 2019-2020)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
20A02	University of South Florida	David Loewenstein, PhD	$ 87,959	03/31/2022	No	Yes	No
20A04	University of Miami	Rosie Curiel Cid, PsyD	$ 86,211	03/31/2022	No	Yes	No
20A05	University of Miami	Hong Jiang, MD, PhD	$ 250,000	03/31/2023	No	Yes	No
20A06	University of South Florida	Lianchun Wang, PhD	$ 250,000	03/31/2022	No	No	No
20A08	University of Florida	Melissa J. Armstrong, MD, MSc	$ 374,660	04/30/2023	No	Yes	No
20A09	Florida State University	Aaron A. Wilber, PhD	$ 250,000	03/31/2024	No	Yes	No
20A10	Mayo Clinic Florida	Pritam Das, PhD	$ 250,000	04/30/2022	No	No	No
20A11	University of Miami	Crocco Elizabeth, MD	$ 248,590	04/30/2022	No	No	No
20A12	University of Miami	Elan Barenholtz, PhD	$ 99,863	04/30/2022	No	No	No
20A13	Albizu University	Miriam J. Rodriguez, PhD	$ 250,000	03/31/2022	No	No	No
20A14	University of Miami	Claes Wahlestedt, MD, PhD	$ 249,959	05/31/2023	No	No	No
20A15	University of Florida	Natalie C. Ebner, PhD	$ 249,930	02/28/2022	No	No	No
20A16	University of Florida	Sara N. Burke, PhD	$ 250,000	03/31/2023	No	No	No
20A17	Florida Atlantic University	Qi Zhang, PhD	$ 100,000	04/30/2022	No	Yes	No
20A18	University of South Florida	Saeid Taheri, PhD	$ 250,000	03/31/2024	No	No	No
20A19	University of Miami	Noam Alperin, PhD	$ 171,790	04/30/2023	No	Yes	No
20A20	Mayo Clinic Florida	Maisha T. Robinson, MD, MS	$ 171,790	03/31/2022	No	No	No
20A21	Mount Sinai Medical Center	Ranjan Duara, MD	$ 171,790	05/31/2022	No	No	No
20A22	Mayo Clinic Florida	Rickey E. Carter, PhD	$ 87,959	03/31/2022	No	Yes	No

1. **Grant #:** 20A02 Postdoctoral Fellowship in Neuropsychology and Neurosciences

Principal Investigator: David Loewenstein, PhD

Organization: University of South Florida

Abstract: Christian Gonzalez-Jimenez, Ph.D. completed one two as a postdoctoral research fellow under the Ed and Ethel Moore AD Program was recently offered and accepted a position as neuropsychologist in his home of Puerto Rico. Two years of postdoctoral training in neuropsychology and cognitive neurosciences is required for Neuropsychology specialty practice. Dr. Gonzalez-Jimenez grew to become a highly valued member of our research team at the Center for Cognitive Neuroscience and Aging (CNSA) at the University of Miami Miller School of Medicine. Due to the fact that South Florida was severely impacted by the COVID-19 pandemic, the University of Miami postponed all onsite evaluations for research participants for over six months. However, the Center developed a successful virtual platform for the administration of neuropsychological evaluations that allowed the continuation of all study-related procedures in a safe and valid manner. Dr. Gonzalez contributed substantially to this effort and worked closely with the faculty to develop training protocols (including training videos

that could be delivered remotely) and detailed manuals following the recommendations provided by the National Academy of Neuropsychology and the National Alzheimer's Coordinating Center in order to transition our research visits to a telehealth platform. Dr Gonzales-Jimenez also contributed significantly to the development of a cross-cultural manual which will be utilized at our center to guide cross-cultural clinical research and clinical evaluations. In addition, Dr. Gonzalez provided direct training and supervision to all research staff regarding teleneuropsychological administration. Dr. Gonzalez-Jimenez has contributed to various scientific manuscripts and posters, which have been peer reviewed and accepted for presentation and publication, respectively. Dr. Gonzalez-Jimenz is currently finalizing with Co-Mentor Dr. Curiel another scientific manuscript that will evaluate data collected in an National Institute of Health study relating MRI markers to performance on novel cognitive measures. Scholarly presentations were also provided, including a very well-accepted presentation at Carlos Albizu University in Puerto Rico, sharing the Center for Cognitive Nueroscience and Aging (CNSA) data and research. In addition, Dr. Gonzalez-Jimenez has recently received more autonomy in terms of the supervision and management of a state funded project, which was successfully completed.

Follow-on Funding: None at the of reporting.

Collaborations: Our center provides a training plataform for pre-doctoral students from several local universities and colleges. Dr. Gonzalez has a crucial role in this aspect as she provides direct supervision to three pre-doctoral students from Carlos Albizu University and five pre-doctoral students from Nova Southestern University who seek neuropsychology training.

Journals: Elizabeth Crocco, M.D.a, Rosie E. Curiel-Cid, Psy.D.ab, Marcela Kitaigorodsky, Psy.D.a, Christian J. González-Jiménez, Ph.D.a, Diane Zheng, Ph.D. a, Ranjan Duara, M.D.bc, David A. Loewenstein, Ph.D.ab A Brief Cognitive Screening Test Detects Prodromal Alzheimer's disease States (Under Review). Journal of Alzheimer's Disease.

Kitaigorodsky M, Loewenstein D, Curiel Cid R, Crocco E, Gorman K, González-Jiménez C. A. Teleneuropsychology Protocol for the Cognitive Assessment of Older Adults During COVID-19. Front Psychol. 2021 May 13;12:651136. doi: 10.3389/fpsyg.2021.651136. PMID: 34054655; PMCID: PMC8155705.

González-Jiménez, C., Gorman, K. L., Lopez-Palacios, D., Garcia-Diaz, M., Raffo, A., Kitaigorodsky, M., Curiel Cid, R., & Loewenstein, D. (2021, February). Deficits in Odor Identification and Susceptibility to Proactive Semantic Interference in Older Adults with Mild Cognitive Impairment. Oral presentation at the Mild Cognitive Impairment (MCI) Symposium, Miami, Florida.

Gorman, K. L., González-Jiménez, C., Lopez-Palacios, D., Garcia-Diaz, M., Raffo, A., Kitaigorodsky, M., Curiel Cid, R., & Loewenstein, D., Deficits in Odor Identification and Susceptibility to Proactive Semantic Interference in Older Adults with Mild Cognitive Impairment. Poster Presentation (2021). American Psychological Association Annual Conference, 2021

Katherine Gorman, Psy.D., Christian González-Jiménez, Ph.D., Cynthia Herrera, M.S., Lubnah Jahjah, M.S., Marcela Kitaigorodsky, Psy.D., Rosie Curiel Cid, Psy.D. & David Loewenstein, Ph.D., ABPP-CN. Poor Sleep Quality is associated with Semantic Intrusion Errors among Cognitively Normal Older Adults. Poster Presentation [Accepted for Presentation]. American Psychological Evaluation Annual Conference, 2020

Patents: None at time of reporting.

2. **Grant #:** 20A04 Postdoctoral Fellowship in Neuropsychology

Principal Investigator: Rosie Curiel Cid, PsyD

Organization: University of Miami

Abstract: Katherine Gorman, PsyD completed Year 2 of the postdoctoral research fellowship under the Ed and Ethel Moore AD Program. Dr. Gorman passed the Florida Laws and Rules examination in order to obtain Florida licensure to practice psychology. Two years of postdoctoral training in neuropsychology and cognitive neurosciences are required to practice in the neuropsychology specialty. Dr. Gorman was offered and accepted a position as a neuropsychologist in New Hampshire. Dr. Gorman demonstrated excellence as a member of our research team at the Center for Cognitive Neuroscience and Aging (CNSA), Psychiatry Department at University of Miami Miller School of Medicine.

Due to the fact that South Florida was severely impacted by the COVID-19 pandemic, the University Of Miami postponed all onsite evaluations for research participants for over six months. However, the center developed a successful virtual platform for the administration of neuropsychological evaluations that allowed the continuation of all study-related procedures in a safe and valid manner. Dr. Gorman contributed significantly to this process. Dr. Gorman participated in the development, modification, and implementation of the CNSA research protocols. Dr. Gorman worked closely with the faculty to develop training videos and manuals for the telehealth administration of our assessments following National Academy of Neuropsychology and the National Alzheimer's Coordinating Center guidelines in order to transition research visits to a telehealth platform. Dr. Gorman also led training for research associates, pre-doctoral students, and research staff members on how to administer virtual assessments. The center has recently resumed onsite evaluations, and biomarker data collection. As such, Dr. Gorman has been contributing significantly to the adaptation of the existing research protocol involving Positron Emission Tomography/Computed Tomography (PET/CT) imaging and other biomarkers related to Alzheimr's and Related Dementias (ADRD) to comply with the COVID-19 safety guidelines and University Protocols. Dr. Gorman has also provided supervision and mentoring for staff members regarding such procedures. During this term Dr. Gorman continued administering, scoring, and interpreting gold standard and novel Neuropsychological measures used among older adults at risk for ADRD. She has also provided mentoring and supervision of all pre-doctoral students.

During this second year, Dr. Gorman contributed to two scientific manuscript and completed three abstracts which were accepted for presentation at the American Psychological evaluation, the Mild Cognitive Impairment (MCI) Symposium, and the Alzheimer's Association International Conference (AAIC). Dr Gorman participated actively in and led the CNSA neuroscience didactic series that is held weekly and includes a multidisciplinary team including geriatric psychiatry fellows, predoctoral externs and medical students. In addition, in order to supplement didactic training during COVID-19, Dr. Gorman completed a fully comprehensive online course called "Behavioral and Cognitive Neurology" taught by the National Neuropsychological society.

Follow-on Funding: None at the of reporting.

Collaborations: Our Center provides clinical research training for pre-doctoral students from several local universities and colleges. Dr. Gorman has a crucial role in this aspect as she provides direct supervision to three pre-doctoral students from Carlos Albizu University and five pre-doctoral students from Nova Southestern University who seek neuropsychology training.

Journals: Miriam J Rodriguez PhD, Katherine Gorman PhD, Rosie Curiel PsyD, Ranjan Duara M.D. & David A. Loewenstein PhD. (Under Review). Diagnostic utility of visual memory tests among older adults at risk for Alzheimer's disease.

Kitaigorodsky M, Loewenstein D, Curiel Cid R, Crocco E, Gorman K, González-Jiménez C. A. Teleneuropsychology Protocol for the Cognitive Assessment of Older Adults During COVID-19. Front Psychol. 2021 May 13;12:651136. doi: 10.3389/fpsyg.2021.651136. PMID: 34054655; PMCID: PMC8155705.

González-Jiménez, C., Gorman, K. L., Lopez-Palacios, D., Garcia-Diaz, M., Raffo, A., Kitaigorodsky, M., Curiel Cid, R., & Loewenstein, D. (2021, February). Deficits in Odor Identification and Susceptibility to Proactive Semantic Interference in Older Adults with Mild Cognitive Impairment. Oral presentation at the Mild Cognitive Impairment (MCI) Symposium, Miami, Florida.

Gorman, K. L., González-Jiménez, C., Lopez-Palacios, D., Garcia-Diaz, M., Raffo, A., Kitaigorodsky, M., Curiel Cid, R., & Loewenstein, D., Deficits in Odor Identification and Susceptibility to Proactive Semantic Interference in Older Adults with Mild Cognitive Impairment. Poster Presentation (2021). American Psychological Association Annual Conference, 2021

Katherine Gorman, Psy.D., Christian González-Jiménez, Ph.D., Cynthia Herrera, M.S., Lubnah Jahjah, M.S., Marcela Kitaigorodsky, Psy.D., Rosie Curiel Cid, Psy.D. & David Loewenstein, Ph.D., ABPP-CN. Poor Sleep Quality is associated with Semantic Intrusion Errors among Cognitively Normal Older Adults. Poster Presentation [Accepted for Presentation]. American Psychological Evaluation Annual Conference, 2020

Patents: None at time of reporting.

3. **Grant #:** 20A05 Retinal Biomarkers for Monitoring Vascular Contributions to Alzheimer's Disease

Principal Investigator: Hong Jiang, MD, PhD

Organization: University of Miami

Abstract: The research team started to recruit study subject in this period from the parental National Institutes of Health (NIH) R01 studies (PIs: Loewenstein R01 AG047649 and Curiel R01 AG05563801A1) for in-person study visits, and 12 study subjects which met the inclusion/exclusion criteria were enrolled and imaged.

Meanwhile, the team continued to recruit study subjects from the Department of Neurology and contacted those study patients which met the inclusion/exclusion criteria. A total of 10 study subjects finished in-person visits. Therefore, total 22 study subjects finished study visits. Meanwhile, the team continued to perform the work, under the scope of work, supported by this

grant, which focused on further analysis of previously acquired data and manuscript preparation.

To determine the effect of different software versions on the measurement of retinal vessel densities using optical coherence tomography angiography (OCTA) in normal subjects, thirty-two eyes of eighteen healthy subjects were imaged using two OCTA devices: the Optovue RTVue and the Zeiss Cirrus. The team found the differences of the vessel density measurements between software versions and between devices. This is the first study to determine that different software versions with various intraretinal layer segmentation methods affect the vessel density measurements.

The team also did a critical review of the literature regarding retinal vascular changes in Alzheimer's disease and its prodromal stages, focusing on functional and structural changes of large retinal vessels (vessels visible on fundus photos) and microvasculature (pre-capillary arterioles, capillary, and post-capillary venules) that are invisible on fundus photos.

The team analyzed previously acquired data to characterize the changes of retinal microvascular density and their relations to cognitive function in the healthy older people without known cognitive impairment after an eight-week high-speed circuit resistance training program (HSCT). This is the first study to reveal that the individual response of the SVD was related to the improvement in the cognition in cognitively normal older people after HSCT.

The team continue to analyze previously acquired data to examine the associations between retinal microvascular density, cognition, and physical fitness in healthy older adults with no reported cognitive decline. This is the first study to reveal the association between retinal vessel density and cognition as measured with Montreal Cognitive Assessment (MoCA) in healthy older adults with no report cognitive decline.

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

Collaborations: One medical student and one undergraduate student at the University of Miami are receiving training.

Journals: Wang H, Hu H, Gregori G, Zhang J, Jiang H, Wang J. The Effect of Software Versions on the Measurement of Retinal Vascular Densities Using Optical Coherence Tomography Angiography. Curr Eye Res. 2020 Oct 30;PubMed PMID: 32767906.

Jiang H, Wang J, Levin BE, Baumel BS, Camargo CJ, Signorile JF, Rundek T. Retinal Microvascular Alterations as the Biomarkers for Alzheimer Disease: Are We There Yet? J Neuroophthalmol. 2020 Oct 28. doi: 10.1097/WNO00000000001140. Epub ahead of print. PMID: 33136677.

Fang M, Strand K, Zhang J, Totillo M, Chen Q, Signorile JF, Jiang H, Wang J. Characterization of retinal microvasculature and its relations to cognitive function in older people after circuit resistance training. Exp Gerontol. 2020 Dec;142:111114. PubMed PMID: 33132156; PubMed Central PMCID: PMC7704902.

Zhang J, Strand K, Totillo M, Chen Q, Signorile JF, Jiang H, Wang J. Improvement of retinal tissue perfusion after circuit resistance training in healthy older adults. Exp Gerontol. 2021 Apr;146:111210. doi: 10.1016/j.exger.2020.111210. Epub 2020 Dec 29. PMID: 33385483.

Fang M, Strand K, Zhang J, Totillo M, Signorile JF, Galvin JE, Wang J, Jiang H. Retinal vessel density correlates with cognitive function in older adults. Exp Gerontol. 2021; 152:111433. PMID: 34091000.

Patents: None at the time of reporting.

4. **Grant #:** 20A06 The Role of Extracellular Tau in Endothelial Cell Biology

Principal Investigator: Lianchun Wang, PhD

Organization: University of South Florida

Abstract: The research team is reporting the following research progress on the Specific Aims.

Aim 1. Delineate the proangiogenic function of tau *in vitro*, ex vivo and *in vivo*.

In preliminary studies reported in the proposal, the team has shown that tau increased Biliary Epithelial Cells (BEC) permeability and promoted BEC proliferation and migration *in vitro*. Tau also robustly induced neovascularization in a Matrigel plug angiogenesis mouse model *in vivo*. From April 4,2020 – June 3,2020, the team examined the effect of tau on endothelial cell morphogenesis on coated Matrigel. Tau potently promoted endothelial cell tube formation, like the positive control VEGF165. From July 1,2020 – September 30, 2020, the team optimized the experimental condition and determined that tau potently induced vascular permeability in mouse brain, comparable to positive control VEGF165. The team has worked to test if the cell surface receptor LRP1 mediates the proangiogenic effect of tau in endothelial cells. From January 1, 2021 – October 30,/ 2021, the team generated endothelial cell-specific Low-Density Lipoproteins (LDL) receptor-related protein 1 (LRP1) knockout mice and observed that deficiency of endothelial LRP1 diminished tau-induced neovascularization *in vivo* in the angiogenesis bioreactor assay.

Aim 2. Delineate the molecular mechanisms underlying the proangiogenic function of tau and its crosstalk with Vascular Endothelial Growth Factor (VEGF) signaling.

In *In vitro* studies the team has determined that tau and VEGF165 mutually inhibit their activity to induce brain endothelial cell migration as shown in Preliminary studies in application. From April 2, 2020 – June 3, 2020, the team worked to optimize cell surface tau binding assay with heparin as testing molecule. Heparin acts in a concentration-dependent manner to inhibit human brain cell surface tau binding. From July 1, 2020 – September 30, 2020, the team extended this study to search for the heparan sulfate proteoglycan that mediates cell surface tau binding and cellular uptake. By proteomics analysis, the team observed that tau pulled down much less cell surface heparan sulfate proteoglycan CD44 from heparan sulfate-deficient mouse lung endothelial cells (the Ext1 knockout cell line) compared to wildtype mouse lung endothelial cells. From October 1, 2020 – January 30, 2021, the team determined both mouse and human brain endothelial cells do not express CD44. To search for the heparan sulfate proteoglycans that mediates proangiogenic tau protein, from January 1, 2021 – June 30, 2021, the team has worked to isolated primary mouse brain endothelial cells. The team can get highly purified mouse brain endothelial cells, but the yield remains very low. The research team needs to further optimize the procedure to get enough cells for the proposed further experiment. The team also carried out angiogenesis array and found that tau significantly downregulated the expression of C-X-C motif chemokine 10 (CXCL10), a chemokine that inhibits angiogenesis.

From July 1, 2021 -October 30, 2021, the team determined that recombinant CXCL10 inhibits tau-induced angiogenesis in the matrigel plug mouse model. Now are moving to generating AAV-CXCL10 which will be used to test if CXCL10 could normalize dysregulated angiogenesis in tau-overexpressing mouse model.

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

Collaborations: None at time of reporting.

Journals: None at time of reporting.

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

5. **Grant #:** 20A08 Communication of Dementia Diagnoses: Investigating Patient, Family, and Physician Experiences and Developing Best Practices

Principal Investigator: Melissa J. Armstrong, MD, MSc

Organization: University of Florida

Abstract: The University of Florida (UF) received Institutional Review Board (IRB) approval for the interviews needed to conduct the Ed & Ethel Moore-funded project (grant number 20A08) on February 11, 2020. Materials were subsequently translated into Spanish and IRB approval was also obtained for the translated materials. Florida Atlantic University and the University of Miami ceded to the UF IRB. With IRB approval, the research team is continuing to recruit through the following approaches: University of Florida, Florida Atlantic University, University of Miami, Alzheimer's Association Trial Match, Florida Medical Association's (FMA) News (email), Research Match, Facebook advertising, Outreach to Florida Memory Disorders Clinics, National Alliance for Caregiving, and Dementia Care and Cure Initiative.

Research staff has completed 45 telephone interviews (19 caregivers, 11 patients, 15 health care professionals). Qualitative analysis of the health care professional interviews is in process. This is expected to yield two manuscripts, both of which are in process. Qualitative analysis of the patient and caregiver transcripts is also in process. Research team members have completed the literature search and begun the analysis process for the literature review that will inform the meeting for Aim 3. Research staff have also begun preliminary planning for the Aim 3 meeting.

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

Collaborations: University of Florida (Gainesville, FL): Melissa J. Armstrong, MD is an Associate Professor in the UF College of Medicine Department of Neurology and the Director of the Mangurian Clinical-Research Headquarters for Lewy Body Dementia at the UF Health Fixel

Institute for Neurological Diseases. Dr. Armstrong co-leads the project with Dr. Carma Bylund. In this role, Dr. Armstrong is responsible for grant management, regulartory activities (e.g. IRB approval), study management and conduct, inter-site communications, recruitment, analysis, and manuscript prepration. Dr. Armstrong directly oversees the research coordinator for this study (Noheli Bedenfield).

Carma Bylund, PhD, is now a Professor in the Department of Health Outcomes and Biomedical Informatics in the UF College of Medicine. She was previously a Professor in the College of Journalism, but recently changed colleges/departments. Dr. Bylund co-leads the project with Dr. Melissa Armstrong. In this role, Dr. Bylund provides support for grant management and regulatory activities, is responsbile for study management and conduct, provides direct oversight of interviews and qualitative analysis, and participates in manuscript preparation. Dr. Bylund also directly oversees the doctoral student who was working on this project and who now continues to work on the project as a post-doctoral associate (Easton Wollney).

Florida Atlantic University (Boca Raton, FL): Mónica Roselli, PhD is a Professor and the Assistant Chair of Psychology in the Department of Psychology. Dr. Rosselli is responsible for overseeing study conduct at Florida Atlantic University (including regulatory issues and coordination with other sites), assisting with recruitment for Aims 1 (patients, caregivers) and 2 (clinicians), and participating in Aim 3, where she will bring her perspective as an experienced neuropsychologist and multicultural researcher. As a cross-cultural neuropsychologist Dr. Rosselli will supervise across sites issues related to competency in conducting cross-cultural clinical work.

Ximena Levy, MD, MPH, MBA is the Director of the Human Research Protection Program at Florida Atlantic University. Dr. Levy assists with regulatory activities (locally and collaborations with other sites), inter-site coordination, recruitment (including initial contact, discussion of study approach, initial review of the consent forms, and coordination with the interview team) of patients and caregivers (Aim 1) and physicians (Aim 2) and coordination with local Aim 3 participants as needed. If the research coordinator has need language proficiencies, she may also be asked to assist in relevant interviews if needed.

Florida Atlantic University has recruited seven participants for the reporting period.

University of Miami (Miami, FL): Rosie E. Curiel, PsyD is an Associate Professor of Psychiatry and Behavioral Sciences and faculty at the University of Miami Center on Aging. She is also Chief of Cross-Cultural Neuropsychology for the CNSA at UM. Dr. Curiel is a bilingual/bicultural neuropsychologist who specializes in the evaluation and diagnosis of diverse cognitively impaired populations. Her research has focused on aging and cognition. Dr. Curiel serves as a co-Investigator for the clinical core of the 1Florida Alzheimer's Disease Research Center and participates in multiple R01s. Dr. Curiel is responsible for overseeing study conduct at the University of Miami (including regulatory issues and coordination with other sites), assisting with recruitment for Aims 1 (patients, caregivers) and 2 (physicians), and participating in Aim 3, where she will bring her unique experiences as a neuropsychologist and working with individuals from varied racial-ethnic backgrounds.

Marcela Kitaigorodsky, PsyD is a bilingual neuropsychologist at the University of Miami CNSA who will work alongside Dr. Curiel to interface with diverse patients and caregivers and physicians. She will also assist with regulatory activities (locally and collaborations with other sites), inter-site coordination, recruitment (including initial contact, discussion of study approach, initial review of the consent forms, and coordination with the interview team).

The University of Miami developed a comprehensive recruitment plan and has recruited 11 participants.

Journals: Armstrong MJ, Weisbrod NJ, Bylund CL. Strategies to improve clinician-patient communication experiences for patients with neurologic conditions. Neurol. Clin. Pract., 2021, published online ahead of print on 4/14/2021. DOI: 10.1212/CPJ00000000001091.

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

6. **Grant #:** 20A09 Cortical-Hippocampal Interactions During Sleep in Alzheimer's Disease

Principal Investigator: Aaron, A, Wilber, PhD

Organization: Florida State University

Abstract: Alzheimer's disease (AD) is devastating for individuals and society. Impaired learning and memory, particularly in the context of spatial navigation (e.g., driving to the new store across town), is one of its major symptoms. Similarly, rodent models of AD also exhibit impairments in spatial navigation. For this proposal, the research team developed and are using a spatial navigation task that mimics the impairments observed in humans (getting lost in new surroundings) in mice. There is a great deal of scientific evidence suggesting abnormal communication between two parts of the brain, the parietal cortex and hippocampus, in humans with AD. The team previously published a paper showing that interactions between the parietal cortex and hippocampus during sleep are critical to form new memories. Changes in these brain interactions during sleep could cause impaired learning in AD, especially in early (pre-symptomatic) stages of disease progression as the team is assessing here. The team achieved part of the original proposal by demonstrating that parietal-hippocampal brain network interactions during sleep are impaired in a triple transgenic mouse models of AD which present with Tau and amyloid pathology. These impaired interactions explained, at least in part, impaired spatial navigation in the same mice. In parallel, the team has begun to use a novel approach to functionally dissect the relative contributions of Tau and Aβ in the hippocampus and parietal cortex to impaired parietal-hippocampal interactions during sleep by reversing the pathology in these brain regions. This approach uses a non-invasive treatment currently in clinical trials in humans. More recently, the team began the proposed experiments confirming these findings in a second mouse model, in which the amyloid beta (Aβ) sequence is replaced with a non-mutated human Aβ sequence, to more closely mimic sporadic Alzheimer's in humans (hAβ-KI). The team has assessed these mice at a variety of time points in order to identify a comparable timepoint, when the spatial reorientation impairments first emerge. The first human clinical trial paper was just published this month and indicates promising results. This research is relevant to public health because it will increase knowledge about the role of changes in the functional interactions between the cortex and hippocampus and use current technologies to perform a functional dissection of Tau and amyloid beta clearance in these critical brain circuits. The proposal will expand the knowledge base and establish a new research platform for understanding the mechanism of impaired memory in AD.

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

Collaborations: We hired a technician to work on this project from Stetson University during their summer break. Otherwise, no additional Florida institutions were involved. Three graduate students and 7 undergraduate students received training and performed research activities as part of this project.

Journals: Stimmell, A. C., Xu, Z., Moseley, S. C., Benthem, S. D., Fernandez, D. M., Dang, J. V., Santos-Molina, L. F., Anzalone, R. A., Garcia-Barbon, C. L., Rodriguez, S., Dixon, J. R., Wu, W., & Wilber, A. A. (2021). Tau pathology profile across a parietal-hippocampal brain network is associated with spatial reorientation learning and memory performance in the 3xTg-AD mouse. Frontiers in Aging, 2, 10. doi:https://doi.org/10.3389/fragi.2021.655015

Cone, A. S., Yuan, X., Sun, L., Duke, L. C., Vreones, M. P., Carrier, A. N., Kenyon, S. M., Carver, S. R., Benthem, S. D., Stimmell, A. C., Moseley, S. C., Hike, D. C., Grant, S. C., Wilber, A. A., Olcese, J. M., & Meckes, D. G., Jr. (2021). Mesenchymal stem cell-derived extracellular vesicles ameliorate Alzheimer's-like phenotypes in the 5XFAD mouse model of amyloid beta aggregation. Theranostics, 11(17), 8129-8142. doi:10.7150/thno.62069

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

7. **Grant #:** 20A10 Detection of Vascular and Inflammatory Plasma Biomarkers in Patients Diagnosed with Obstructive Sleep Apnea and Cerebral Small Vessel Disease

Principal Investigator: Pritam Das, PhD

Organization: Mayo Clinic Florida

Abstract: Measure changes in vascular, inflammation biomarkers and neurofilament light chain in the plasma of patients diagnosed with Obstructive Sleep Apnea (OSA) with varying degrees of Cerebral Small Vessel Disease (CSVD) pathology using the Mayo Clinic Familial Cerebrovascular Diseases Registry (IRB: 08-003878).

Using the Enzyme Linked Immunosorbent Assay (ELISA), the research team now show some significant gender specific changes with a subset of markers. For example, in male OSA patients that had a stroke, there was an increase in both C-X-C motif chemokine 10 (CXCL10) and interleukin 10 (IL-10) (increases were found specifically in males, with more plasma levels in cases with more severe white matter pathology). Significantly, the team also found that Angiopoetin-1, an important protein involved in vascular integrity and angiogenesis, was decreased in male OSA patients that had a stroke, with lower plasma levels in cases with more severe white matter pathology. This is a significant finding that the team is currently further pursuing using additional plasma samples from stroke patients. For example, to determine whether lower expression levels of Angiopoetin-1 could also increase risk for stroke, the team is currently analyzing plasma levels in a larger cohort of stroke samples using the Mayo Clinic Familial Cerebrovascular Diseases Registry (IRB: 08-003878). And significantly the team has identified several samples including plasma from unaffected family members, which will aide in this type of association studies.

Perform a pilot prospective longitudinal study to measure changes in plasma biomarkers, cognitive impairment and white matter pathologies in OSA patients enrolled in the Mayo Clinic sleep center. Name of Study: Detection of Vascular and Inflammatory Plasma Biomarkers in Patients Diagnosed with Obstructive Sleep Apnea and MRI-defined Cerebral Small Vessel Disease. IRB # 20-000692. Phase # prospective, single-center, longitudinal cohort study.

The team has now generated some preliminary data from plasma of seven OSA patients enrolled in this study from various timepoints of collection. This analysis shows that in five out of the seven patients, there was increased plasma levels of Vascular Endothelial Growth Factor

(VEGF-A), suggesting underlying hypoxia/oxidative stress. The team also demonstrated a differential response in some patients (e.g., OSA patient # 2, 4 and 7) that show increase levels of Placenta-like Growth Factor (PlGF), VEGF-D and inflammatory cytokine Tumor Necrosis Factor (TNF)-alpha. OSA patient #2 also showed increased CXC10 levels. The team continue to collect plasma and have now enrolled additional patients for the Aim. The team will update on plasma markers in the next cycle using these additional patient samples and more times points.

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

Collaborations: None at time of reporting.

Journals: None at time of reporting.

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

8. **Grant #:** 20A11 Building an Advanced Cognitive and Biomarker Registry for African American Older Adults At-Risk for Alzheimer's Disease

Principal Investigator: Crocco Elizabeth, MD

Organization: University of Miami

Abstract: The study team continues to work diligently in recruitment efforts by identifying prospect study participants, reaching out to community partners to share the team's ongoing research projects and offer community education, organizing virtual webinars, education forums, and presentations targeted to older adults in conjunction with community partners (e.g. Alzheimer's Florida Association) to increase awareness about brain health and promote the activities performed at the Center. During this reporting period, an additional four outreach presentations/events were with a combined total of 21 outreach presentations/events with an attendance of over 2,285 individuals since project start up.

All planned project start-up procedures have been completed successfully. The research personnel have been hired, the study has obtained Institutional Review Board (IRB) approval, and the infrastructure for neuroimaging and blood collection has been established. This includes all standard operating procedures that ensure mandatory compliance with restrictions imposed by the COVID-19 pandemic.

Outreach and recruitment efforts have been made including contact with local community partners that will facilitate the recruitment of participants for this study. The study timeline was delayed in the initial planned recruitment efforts due to the COVID-19 pandemic; however, as of October 2020, the team received the institutional approval to resume all in-person outreach, imaging, blood work and clinical and neuropsychological evaluations. In addition to in-person visits, the team has the option to use a hybrid model that facilitates neuropsychological evaluations in a valid manner for participants who prefer to complete this study procedure virtually. To date, 30 participants have been enrolled in the study; 11 during this reporting period.

The study team continues to work diligently in recruitment efforts by identifying prospect study participants, reaching out to community partners to share the ongoing research projects and offer community education, organizing virtual webinars, education forums, and presentations targeted to older adults in conjunction with community partners (e.g. Alzheimer's Florida

Association) to increase awareness about brain health and promote the activities performed at the Center. During this reporting period, an additional four outreach presentations/events were with a combined total of 21 outreach presentations/events with an attendance of over 2,285 individuals since project start up.

Follow-on Funding: None at the time of Reporting.

Collaborations: There are two Ed and Ethel Moore Postdoctoral Research Fellows that have been trained on all aspects of the study and will be collaborating with PI Crocco on this research project, receiving clinical research training and performing study-related duties.

Pre-doctoral practicum students: there are four-five pre-doctoral students from Nova Southeastern University, College of Psychology, Clinical Psychology Program. Students assist in research activities as part of their one year practicum experience.

Pre-doctoral practicum students: there is one pre-doctoral student from Carlos Albizu University-Clinical Psychology Program who assists in the research activities as part of his one year practicum experience.

Journals: None at time of reporting.

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

9. **Grant #:** 20A12 Development of a Gaze and Speech-Behavior Based Cognitive Exam to Assist in the Detection of Early-Stage Alzheimer's Disease and Related Disorders

Principal Investigator: Elan Barenholtz, PhD

Organization: University of Miami

Abstract: This research involves developing an experimental protocol for assessing gaze and speech behavior in dementia patients with minimal input and oversight from medical professionals, easing the time and cost requirements for routine screening. The protocol will be tested in a population of patients with very mild and mild Alzheimer's disease as well as healthy controls, to determine its effectiveness and accuracy levels. As a result of COVID-19 related delays, participant recruitment has been significantly impacted and the opening of the neurology lab space at University of Miami, where participant testing must occur, has been pushed back. However, progress has been made establishing the experiment protocol and procedure and preparing for data analysis. Recruitment is expected to begin before the end of the year.

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

Collaborations: The University of Miami (Miami, FL) Miller School of Medicine's Comprehensive Center for Brain Health, located within the Department of Neurology, is responsible for participant recruitment, data collection, experiment generation, and data analysis. Dr. Michael Kleiman, the Postdoctoral Research Fellow, is in charge of all proceedings concerning this grant at this lab space. The Director of the Comprehensive Center for Brain Health, Dr. James Galvin, manages overall participant recruitment and enrollment into the Center's pool of healthy and impaired participants, from which this grant's participants are recruited.

Journals: None at the time of reporting.

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

10. **Grant #:** 20A13 Relationship Between Functional measures, Cognitive Performace, and Alzheimer's Disease Biomarkers Between Hispanic and White Non-Hispanic

Principal Investigator: Miriam J. Rodriguez, PhD

Organization: Albizu University

Abstract: Few studies have examined relationships between Alzheimer's Disease (AD) biomarkers and functional measures among various ethnic groups. With this application, the research team propose to examine the following functional measures: AD Cooperative Study Mild Cognitive Impairment (ADCSMCI).

The team is introducing an additional functional scale to the Activities of Daily Living (ADL) (Galasko, 1998), and the modified Clinical Dementia Rating (CDR) scale (mCDR; Duara et al, 2010). The latter uses a multiple-choice response format across the same six functional domains from the CDR, but unlike the CDR, the mCDR does not include any objective testing of memory. Preliminary comparisons between the CDR and mCDR by the 1Florida Alzheimer's Disease and Related Conditions (ADRC) indicated the mCDR better predicted the transition from CN to Mild Cognitive Impairment (MCI), whereas the CDR better predicted transition from MCI to AD.

The current pandemic has negatively affected recruitment for the current study. The current study was funded in 2020 when quarantine and social distance directives were put in place. Older adults have been identified to be one of the most vulnerable populations to infection and poor prognosis from the COVID-19 virus. The recruitment facility has limited the number of personnel on campus and volunteers and non-essential personnel have been restricted. These factors have significantly impacted recruitment for this study. However, these challenges were addressed by changing the protocol so that administration of the functional measures are now taking place via telephone instead of in person. Recruitment efforts were slow, but this study will have a large enough sample size by November for preliminary analyses and dissemination of results through poster presentation at the Alzheimer's Association International Conference.

The relationship of functional measures to cognitive performance, MRI volumetric analysis, Amyloid imaging, and Apoe4 carrier status will be examined among Hispanic and white non-Hispanic participants. Results of the proposed study will be an important contribution to understanding the effect of biomarkers, cognition, and ADL and Instrumental Activities of Daily Living (IADL) function among multiethnic groups. The study will help identify effective functional measures that can be used among Hispanics to diagnose and evaluate functional progression in AD and other dementias, especially in the prodromal stages when treatment can be most effective.

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

Collaborations: None at time of reporting.

Journals: None at time of reporting.

Patents: None at the time of reporting.

11. **Grant #:** 20A14 Contributions of Histone Deacetylase 8 (HDAC8) to Alzheimer's Disease Pathogenesis

Principal Investigator: Claes Wahlestedt, MD, PhD

Organization: University of Miami

Abstract: The purpose of this project is to validate whether increased histone deacetylase-8 (HDAC8) activity can prevent and/or rescue Alzheimer's disease (AD)-like pathogenesis in AD models. The research team will use both genetic (plasmid-mediated) and pharmacological interventions to increase or inhibit HDAC8 activity. These studies will help confirm whether HDAC8 upregulation is a suitable target for AD and whether inhibition of this HDAC isoform should be avoided. Context and progress to date: This is a three-year grant that was fully executed in June 2020. The research staff has bought reagents and started conducting experiments on brain cells. Considering the recent shortcomings of AD clinical trials, the research project team and others have proposed targeting epigenetic enzymes as a potential therapeutic approach for AD. One such group of enzymes is Class I HDACs comprising of four members: HDACs 1, 2, 3 and 8. The research staff and others have shown that inhibition of HDACs 1, 2 and 3 can individually present beneficial effects for AD by either increasing neuroprotective genes such as brain-derived neurotrophic factor (BDNF), reducing AD-like pathogenesis and/or increasing learning and memory in animal models. Remarkably little has been shown about the effects of HDAC8 activity on AD-like pathogenesis, although inhibition of HDAC8 has been well-documented as a drug target for the treatment of various types of cancers. Using validated tools from the HDAC8 cancer field, such as shRNAs and the selective HDAC8 inhibitor PCI-34051, our preliminary data unexpectedly suggest that interrupting HDAC8 signaling potentially aggravates AD-like pathogenesis. Indeed, following silencing of HDAC8 in an AD cell model, the team observed significant increases in expression of AD-related genes such as beta-secretases and gamma-secretase complex components, while noting decreases in BDNF mRNA levels. At the protein level, the team also found decreased BDNF, increased tau phosphorylation, increased Abeta1-42 and increased sAPPbeta (a cleavage product of beta-secretase) - all contributors to AD hallmarks in patients' brain. Conversely, when the team increased HDAC8 expression in the brain of wild type mice, the team observed increases in BDNF and phosphorylated cAMP element binding protein (CREB), both key components of learning and memory formation. These data support the hypothesis that HDAC8 activity is neuroprotective and potentially beneficial for Alzheimer's disease. The research team thus hypothesizes that an HDAC8 activator will be protective against AD and result in increased cognitive performance in AD animal models. To date, the team has validated our HDAC 8 plasmids, showing that they increase HDAC8 activity in brain cells. The team has also demonstrated that increased BDNF expression correlates with decreased HDAC8 enzymatic activity in brain cells. Impact to Floridians: In the state of Florida, approximately half a million people currently suffer from AD. Data from the proposed work can validate whether increasing HDAC8 activity is protective and a novel therapeutic strategy for AD, and potentially yield a small molecule HDAC8 activator suitable for AD treatment in Florida and beyond.

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

Collaborations: The PIs (Department of Psychiatry and Center for Therapeutic Innovation), two graduate students (Department of Neuroscience and Programs in Biomedical Sciences (PIBS) and Department of Molecular and Cellular Pharmacology) all at the University of Miami Miller School of Medicine and two undergraduate student (University of Miami Coral Gables Campus) have been involved with this research project.

Journals: None at time of reporting.

Patents: None at the time of reporting.

12. **Grant #:** 20A15 Evaluating Neurofeedback-Induced Plasticity to Improve Spatial Navigation Behavior in Older Adults at Risk for Alzheimer's disease

Principal Investigator: Natalie C. Ebner, PhD

Organization: University of Florida

Abstract: In addition to cognitive changes, aging is associated with emotional changes, such as loss of interest in activities and lowered responding to emotional cues. These emotional changes occur in normal aging and tend to be pronounced (e.g., affective blunting, general apathy) in age-related neurodegenerative disorders such as Alzheimer's Disease (AD). In addition to psychosocial factors (e.g., loss of spouse), there is evidence that age-related dampening of neural responses in brain regions crucially involved in emotion processing (i.e., anterior insula, dorsal anterior cingulate cortex) may underlie emotional deficits in aging. However, to date, processes in the brain underlying emotional deficits and the extent to which they are malleable in older adults and in age-related pathology are not well studied. Emotional health is relevant to people across all ages. Thus, it is vital to understand the extent to which emotions change as individuals grow older and to determine processes involved in effective regulation on the level of brain and behavior. To fill this research gap, the research team applied the innovative technology of real-time functional magnetic resonance imaging (rtfMRI), which the group has implemented at University of Florida for use in older adults, to directly test brain-behavior relationships. The specific aims are twofold: to examine whether at risk for developing AD can learn to regulate brain activity in a target region of interest and to test whether increasing brain activity in this target region improves response to emotional cues. The team will assess patients' brain activity in real time and give them continuous feedback about how active it is. The team will train patients to increase or decrease target activity (vs. a control) when asked to do so; and the team will test to which extent up-regulation of this targeted brain activity will improve emotion processing. To date the team has almost completed data collection, with just a few currently enrolled participants finalizing the training scheme this month. Preliminary data provide support for Aim 1 but full sample data analysis must confirm these promising first results and test hypotheses under Aim 2. This preliminary data has been leveraged in two National Institutes of Health R01 submissions (one scored at the second percentile and pending funding decision; and the other pending scientific merit review in October). Knowledge gained from this project will advance scientific understanding of the basic mechanistic chain underlying emotion processing in healthy and pathological aging. In addition, this project will implement rtfMRI as a novel neuroimaging technique for the study of brain-behavior connections in clinical older populations.

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

Collaborations: The University of Florida is involved in this research project, providing institutional resources to support scanning, behavioral testing, and grant administration. This proposal is providing research experience for 1 postdoc, 2 graduate students, and 2 post-bac trainees.

Journals: None at time of reporting.

Patents: None at the time of reporting.

13. **Grant #:** 20A16 Cyclic Ketogenic Therapy as Treatment for Alzheimer's Disease-Related Metabolic Decline, Tau Pathology and Cognitive Impairments

Principal Investigator: Sara N. Burke, PhD

Organization: University of Florida

Abstract: A defining feature of Alzheimer's disease is a reduced ability of the brain to use glucose to meet its energetic needs. Relatedly, there is a well-established link between insulin resistance and the risk of developing Alzheimer's disease. Within the brain, dysfunctional insulin signaling can promote the pathological aggregation of tau protein that ultimately leads to neurodegeneration, brain atrophy and cognitive loss. The research team's pilot data, and the work of others, shows that high fat/low carbohydrate ketogenic diets have enormous potential for improving brain metabolism and enhancing cognitive function. Ketogenic diets increase circulating and brain levels of ketone bodies that can substitute for glucose in the production of energy. While glucose utilization in the brain is impaired in Alzheimer's disease, the utilization of ketone bodies remains intact. Thus, ketogenic diet therapy is likely to improve brain metabolism in individuals with Alzheimer's disease thereby changing the disease course and enhancing cognitive function.

A major barrier to the implementation of nutritional ketogenic therapy, however, is low compliance associated with long-term carbohydrate restriction in Alzheimer's disease patients that have increased cravings for high carbohydrate, sweet foods. The objective of this proposal, which has not changed since the initial funding, is to restore brain metabolism in a rat model of age-related metabolic syndrome and Alzheimer's disease-related tauopathy with a cyclic ketogenic diet. Cyclic ketosis allows for windows in which one can consume carbohydrates thereby showing greater translational potential than a standard continuous ketogenic diet. In this last reporting period, research staff have observed that once rats establish stable levels of ketosis over four weeks of a high fat/low carbohydrate diet, they can readily switch back into ketosis within 24 hours following a week of consuming a standard carbohydrate diet, and this is associated with improved cognitive function. These data are being obtained from a rat model because this allows for precise control of caloric and micronutrient intake, which is difficult in community dwelling populations.

Moreover, research state are using sophisticated cognitive testing with touchscreen tasks that have been adapted from neuropsychological assessment in humans for use in rodents. Based on the preliminary data collected to date, the central hypothesis that after establishing stable ketosis for four weeks, 12 weeks of cycling on and off a ketogenic diet with one-week intervals will be sufficient to normalize brain metabolism in rats with metabolic syndrome and tau pathology is being evaluated with the following aims: determine if a cyclic ketogenic diet

regimen can mimic long term nutritional ketosis, and determine if cyclic ketosis can improve cognitive function in rats with tau pathology. This work is significant because the successful completion of these aims will establish a novel therapeutic strategy with greater feasibility and translational potential than standard ketogenic diet therapies. Critically, ketogenic diet cycling is an accessible lifestyle modification that can be rapidly implemented in persons with Alzheimer's disease and populations at risk.

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

Collaborations: None at time of reporting.

Journals: None at time of reporting.

Patents: None at the time of reporting.

14. **Grant #:** 20A17 Amyloid Precursor Protein And Cholesterol As A Novel Druggable Axis For Alzheimer's Disease

Principal Investigator: Qi Zhang, PhD

Organization: Florida Atlantic University

Abstract: Aim 1: Establish iN-based platform to test how familial Alzheimer's Disease (AD) mutations affect neuronal mChol. Using immunocytochemistry, electrophysiology, live-cell imaging, the team has confirmed that the neuron-like cells differentiated from the wildtype and the Amyloid precursor protein (APP)-knockout human iPSCs possess all features of neurons being tested. The team named those cells induced human neurons (hiNs). Using those two groups of hiNs, the team first tested the membrane cholesterol (mChol) content using two refined Filipin staining protocols targeting surface and total mChol separately. In both cases, the team also co-applied a pan-membrane dye (AM1-43) to measure surface or total membrane area, which is a normalization measure in order to control the variation of membrane areas. The team found significantly less surface mChol in APP-null hiNs than wildtype control. Next, we used a new mChol reporter as well as two existing methods to examine mChol homeostasis especially in neuronal synapses, and the team found that the lack of APP significantly delayed mChol retrieval from surface membrane, which induced a reduction of overall surface mChol likely as a compensatory measure by neurons. Then, the team tested five APP mutants bearing representative fAD mutations. The project staff did find that point mutations affecting APP's affinity to mChol or its surface membrane localization have phenotypes resembling those in APP-null cells. Now, the team's continuous efforts are to test more fAD mutations and new mutations targeting on mChol-binding, APP trafficking and its C-terminal fragment.

Aim 2: Examine how direct manipulation of neuronal mChol affect APP and AD-like pathology. Using novel fluorescent mChol reporters, the team quantitatively assess the effects of drugs and protein factors that can alter Chol synthesis, uptake, transport, dispersion, and catabolism. Moreover, the staff are combining those reporters with other neuronal and synaptic markers to perform live-cell imaging of mChol trafficking and synaptic transmission in live hiNs. The staff has found that exhaustive stimulations challenge neurons ability to maintain mChol homeostasis, especially at synaptic terminals. Similarly, reduction of Chol synthesis or uptake, disruption of intracellular mChol transport to surface membranes, and removal of surface mChol all increase the burden of mChol homeostasis. While wildtype hiNs can reasonably sustain

those challenges to certain degree, APP-null or mutant-expressing ones are vulnerable and cannot sustain for long or when some of those challenges are combined. Moreover, the staff is employing immunostaining, electrophysiology and live-cell imaging to probe how the dysregulation of mChol homeostasis is affecting neuronal functions, especially synaptic transmission and plasticity in the wildtype and APP-null or mutant hiNs.

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

Collaborations: Postsecondary educational institutions involved: Vanderbilt University: We have built collaboration with Dr. Charles R. Sanders at Vanderbilt University. Dr. Sanders' postdoctoral trainee, Dr. Hui Huang, has been participating this project by helping us on generating APP mutants in viral vectors for application on hiNs *in vitro* as well as micro-injection *in vivo*. Number of students receiving training or performing research under the research project: 5.

Journals: Alamgir, S., Pelletier, O. B., Thomas, D., Rubio, V., Stawikowski, M. J., Zhang, Q. Measuring Membrane Lipid Turnover with the pH-sensitive Fluorescent Lipid Analog ND6. J. Vis. Exp (173), e62717, doi:10.3791/62717 (2021).

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

15. **Grant #:** 20A18 Impact of Cerebrovascular Pathology on Alzheimer's Disease and Other Dementia

Principal Investigator: Saeid Taheri, PhD

Organization: University of South Florida

Abstract: In most of age-related cognitively declined multiple pathologies coexist that vary across the aging spectrum. The manifestation of these pathologies can be observed via various biomarkers, including behavioral and psychological symptoms, *in vivo* imaging, cerebrospinal fluids and blood markers.

However, behavioral and psychological symptoms, as leading markers, have different prevalence onset and course. Therefore, the course, onset and pattern of biomarkers on cerebrovascular pathology are valuable tools in understanding the disease. The research staff hypothesize that longitudinal epidemiological data of cerebrovascular pathologies aid in understanding the role of vascular pathology in Alzheimer's Disease (AD). To tests this hypothesis the staff will recruit cognitively impaired patients with and without the symptoms of AD and investigate the current state of disease by using Magnetic Resonance Imaging (MRI) and biochemical data, along with epidemiological data. Knowledge about the impact of vascular disease on AD enables us to tailor treatments.

Progress:

1- The research team has phone interviewed more volunteers for recruiting to our study.

2- The team recruited more patients into the study by taking informed consents.

3- The team is adjusting the imaging protocols on a Philips 3T magnet at University Diagnostic Imaging (UDI) center.

4- The team is working more closely with Dr. Gopal Thinakaran as one of the advisors to the study.

5- The team prepared a proposal for Nov 12 submission for NIH Funding opportunity, Research on Current Topics in Alzheimer's disease and Its Related Dementias (R21, PAR-19-071; November 12 2021).

6- The team is working on the data that that was acquired from the National Alzheimer's Coordinating Center's (NACC). There are promising signs that theteam can used NACC data along with our data on the brain injury impacts on dementia.

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However, behavioral and psychological symptoms, as leading markers, have different prevalence onset and course. Therefore, the course, onset and pattern of biomarkers on cerebrovascular pathology are valuable tools in understanding the disease. The team has hypothesize that longitudinal epidemiological data of cerebrovascular pathologies aid in understanding the role of vascular pathology in AD. To tests this hypothesis the team will recruit cognitively impaired patients with and without the symptoms of AD and investigate the current state of disease by using MRI and biochemical data, along with epidemiological data. Knowledge about the impact of vascular disease on AD enables the ability to tailor treatments.

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

Collaborations: None at time of reporting.

Journals: None at time of reporting.

Patents: None at the time of reporting.

16. **Grant #:** 20A19 Lifestyle Stressors of Hippocampus and Alzheimer's Disease Related Brain Regions: Potential for Intervention

Principal Investigator: Noam Alperin, PhD

Organization: University of Miami

Abstract: The following abstract summarizes the research team's most important research findings. The team started with recruitment of healthy older adults who suffer from poor sleep. The study assesses the effect of cognitive behavior therapy toward improving sleep quality and thereby slowing down the rate of tissue loss in cognitive critical brain regions, which in turn is likely to delay onset of cognitive impairments. Poor sleep quality is a known risk factor for Alzheimer's disease. This longitudinal imaging study aimed to determine the acceleration in the rates of tissue loss in cognitively critical brain regions due to poor sleep in healthy elderly individuals. Cognitively normal healthy individuals, 60 years and older, reported Pittsburgh Sleep Quality Index (PSQI) and underwent baseline and two-year follow-up Magnetic Resonance Imaging (MRI) brain scans. The links between self-reported sleep quality, rates of tissue loss in cognitively critical brain regions and white matter hyperintensity (WMH) load were

assessed. Forty-eight subjects were classified into normal (n=23; PSQI<5) and poor sleepers (n=25; PSQI≥5). The two groups were not significantly different in terms of age, gender, years of education, ethnicity, handedness, body mass index, and cognitive performance. Compared to normal sleepers, poor sleepers exhibited much faster rates of volume loss, 2.8-fold in the hippocampus and 3.3-fold in the posterior cingulate over two years. In contrast, there were no significant differences in the rates of volume loss in the cerebral and cerebellar gray and white matter between the two groups. Rates of volume loss in the right hippocampus and right posterior cingulate cortex were negatively associated with global Pittsburgh Sleep Quality Index (PSQI) scores. Poor sleep significantly accelerates volume loss in the right hippocampus and the right posterior cingulate cortex. These findings demonstrate that self-reported sleep quality explains inter-individual differences in the rates of volume loss in cognitively critical brain regions in healthy older adults, and provide a strong impetus to offer sleep interventions to cognitively normal older adults who are poor sleepers.

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

Collaborations: None at time of reporting.

Journals: Liu C, Lee S, Lowenzstien D, Galvin J.E. Alperin N., Poor Sleep Accelerates Hippocampal and Posterior Cingulate Volume Loss in Cognitively Normal Healthy Older Adults (Sleep Research, in press)

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

17. **Grant #:** 20A20 Between Here and There: Addressing End-of-Life Disparities Among African Americans with Mild Cognitive Impairment and Dementia Through Community-Based Training in Advance Care Planning

Principal Investigator: Maisha T. Robinson, MD, MS

Organization: Mayo Clinic Florida

Abstract: Although advance care planning (ACP) in the United States in general occurs less frequently than it should, there is a notable difference in the completion of advance directives based on race/ethnicity that raises a specific, further concern about end-of-life disparities. African Americans with dementia are less likely to complete advance directives and less likely to desire comfort care at the end of life, resulting in more aggressive, non-beneficial medical care. Yet, African Americans are less satisfied than Caucasians with their care at the end of life. The goal of this project is to reduce disparities in end- of-life care by increasing engagement in advance care planning among African Americans with mild cognitive impairment and early dementia and their caregivers.

The research team is working toward identifying ACP barriers and needs of African Americans with early dementia and their caregivers in Jacksonville. The research team will survey 50 African American residents of Jacksonville who have mild cognitive impairment or dementia or who are caregivers of people with dementia about their current practices and perceived barriers around ACP and engage a subset of these participants in focus groups. The survey data revealed that although the respondents were confident that they could ask someone to be their medical decision-maker and discuss their wishes with them, the research subjects were not yet ready to do so. The subjects were also contemplative about completing official documents to

name a health care surrogate and to outline their end-of-life wishes. The focus group data analysis is pending. To refine a culturally relevant community education program on ACP for African Americans. The team will utilize the data collected under Aim 1 to collaborate with Jacksonville residents to refine the content for a standardized and structured culturally-relevant ACP education program.

A working group with members from Mayo Clinic, Jacksonville community, people with mild cognitive impairment and caregivers, and ACP facilitators was assembled to develop a framework for a larger group meeting that will be aimed at increasing knowledge about ACP and completing advance directives. To implement the ACP program developed under Aim 2 and measure its impact. We will train 5 African American community volunteers through a train-the-trainer model to deliver a standardized ACP program to community residents with dementia and their caregivers in group settings. The team hypothesize that knowledge about the components of ACP, readiness to discuss ACP wishes with family members and health care providers, and completion of advance directives will improve following completion of the education program.

Three participants from the Working Group were trained to be facilitators for the larger community meeting.

Outcome Measures: A pre-test assessing baseline knowledge of ACP, session attendance, a post-test assessing acquisition of knowledge the number of completed advance directives, the feasibility and acceptability of the intervention. This intervention has the potential to improve end-of-life care planning and to reduce health care disparities at the end of life in a cohort of people who have expected further cognitive decline and who are disproportionately underutilizing advance directive documents.

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

Collaborations: None at time of reporting.

Journals: None at time of reporting.

Patents: None at the time of reporting.

18. **Grant #:** 20A21 Utility of Blood Biomarkers for Amyloid, Tau and Neurodegeneration to assist in the Diagnosis of Alzheimer's disease and other Dementias - Relationship to Cognition, Brain Atrophy and Amyloid Load

Principal Investigator: Ranjan Duara, MD

Organization: Mount Sinai Medical Center

Abstract: The purpose of this grant is to validate biomarkers from relatively inexpensive blood tests that can detect the presence of Alzheimer's Disease (AD) pathology in the brain at an early stage, even before overt memory impairment. If validated in the diverse 1Florida Alzheimer's Disease Research Center (ADRC) cohort at Mount Sinai Medical Center, it would give specialists and primary care physicians an inexpensive tool for diagnosing AD.

In living individuals, the pathology and signs of AD are currently assessed using expensive brain imaging techniques, such as structural Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) scans. AD pathology can also be measured from an invasive

lumbar puncture using cerebrospinal fluid measures of brain atrophy (plasma neurofilament light, pNfL) and the two hallmark proteins associated with AD: amyloid protein (aß 40 &42) and hyperphosphorylated tau protein. Recently, techniques have been developed to measure these two AD proteins in blood, in addition to other markers of brain degeneration. The research team has shown that pNfL may have a complementary and supportive role to cognitive testing and expensive brain imaging in a memory disorder evaluation. However, the clinical utility of pNfL as a marker of neurodegeneration is limited by its lack of specificity for AD since disorders such as frontotemporal lobe degeneration (FTLD) also evidence elevated levels of pNfL.

Preliminary studies have shown that measures of amyloid and tau proteins in the blood accurately distinguish AD from other neurodegenerative diseases and hold promise as an early preclinical marker for AD. However, more studies are needed to validate this in populations that are diverse with respect to demographics (e.g., Hispanics and African Americans) and diagnosis (e.g., depression). More research is also needed to evaluate how well these plasma biomarkers predict progression of disease. In this current Ed and Ethel Moore study, The team is leveraging the resources of the 1Florida ADRC by collecting blood samples from 150 participants with and without memory impairment, who come for annual follow-up evaluations and have already had, or will have, clinical and neuropsychological assessment, MRI scans and Amyloid PET scans. Our collaborators ate the University of Florida (UF) will analyze our samples using the latest technology from a leader in the field of blood biomarkers, Quanterix. Thus far, the team has collected and shipped 17 samples to UF for analysis. As the pandemic appears to be ending, the team expects to significantly increase enrollment into this study in the coming months.

This study could have a major impact on the health of Florida's elderly population, by detecting AD pathology through a simple blood test, and instituting measures which can delay the rate of disease progression and improve the quality of life of patient with AD and their families, in an ethnically diverse population. Since neuroimaging tests are expensive, pNfL and other blood biomarkers could be an accessible tool in primary care for differentiating those patients presenting with cognitive complaints who have neurodegenerative disorders such as AD versus those who present with treatable disorders (e.g., depression) or are cognitively normal (e.g., the "worried well").

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

Collaborations: There is collaboration with the University of Florida through the use of their recently purchased Quanterix machine. This will be used on blood drawn from ADRC participants to study biomarkers. Furthermore, there is also collaboration with the University of California-San Diego (UCSD) for Dr. Zvinka Zlatar's NIH R01 grant, which studies, "Subjective Cognitive Decline in Older Hispanics/Latinos." Subjects from the 1Florida ADRC will be enrolled into her study to leverage the clinical and imaging data from the ADRC, along with the biomaker data collected from this Ed and Ethel Moore protocol.

Journals: None at time of reporting.

Patents: None at the time of reporting.

19. **Grant #:** 20A22 Racial and Ethnic Differences in Gene Expression Data

Principal Investigator: Rickey E. Carter, PhD

Organization: Mayo Clinic Florida

Abstract: 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 ethnoracial 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 ethnoracial groups remains poorly understood. Thus, clinical, genetic, and neuropathologic differences were investigated in Alzheimer's disease (AD) across three ethnoracial groups from the Florida Autopsied Multi-Ethnic (FLAME) study.

Family history review was also completed, as this may be an important factor to consider when evaluating survival. This cohort contains Hispanic/Latino (n = 67), black/African American (n = 19), and white/European American (n = 1539) patient tissue. To assess family history, a family history of cognitive problems was recorded if noted in the clinical history. Information on individuals whose primary relative (mother, father, sibling) or secondary relative (grandparent, aunt, uncle, cousin) was identified to have cognitive problems was separately recorded. Proportionally Hispanic decedents may have a higher frequency of family members with cognitive problems, whereas black decedents may have a lower frequency.

The objectives of this study are to obtain gene expression data on minority groups and assess differences in gene expression in Alzheimer's disease across ethnoracial groups. To achieve these objectives, the research team has focused on high quality total RNA extraction from frozen hippocampal tissue cases chosen for genetic analysis using state of the art equipment and best laboratory practices. From the prepped ethnoracial minority cases, 75% of cases the team has seen RNA degradation likely due to age of sample and other factors such as post-mortem delay at autopsy and freeze/thaw due to the archival nature of the tissue. Re-extraction has been an ongoing process. The second aim for this research is to apply a previously developed artificial intelligence model, which has been used on white/European American patient tissue, to the Hispanic/Latino and black/African American cohorts to directly test if the patterns of gene expression differ by ethnoracial groups.

The results of this research will be disseminated broadly in order to stimulate new discoveries and providing an optimal diagnosis process for patients with early signs of Alzheimer's disease.

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

Collaborations: None at time of reporting.

Journals: Matchett, B.J., Grinberg, L.T., Theofilas, P. et al. The mechanistic link between selective vulnerability of the locus coeruleus and neurodegeneration in Alzheimer's disease. Acta Neuropathol 141, 631–650 (2021). https://doi.org/10.1007/s00401-020-02248-1

Crist, A.M., Hinkle, K.M., Wang, X. et al. Transcriptomic analysis to identify genes associated with selective hippocampal vulnerability in Alzheimer's disease. Nat Commun 12, 2311 (2021). https://doi.org/10.1038/s41467-021-22399-3

Crist A.M., Hinkle K.M., Wang X., Lesser E.R., Moloney C.M., Azu N.O., Frankenhauser I., Labuzan S.A., Matchett B.J., Liesinger A.M., Serie D., DeTure M., Tang X., Petersen R.C., Duara R., Graff-Radford N.R., Allen M., Carrasquillo M.M., Li H., Ross O.A., Ertekin-Taner N., Dickson D.W., Asmann Y.W., Carter R.E., Murray M.E. (2020) Leveraging selective vulnerability of the hippocampus in Alzheimer's disease subtypes 1 reveals SERPINA5 as a novel tau binding partner. Nature Communication (Accepted) – bioRxiv 2020.12.18.423469

Patents: None at the time of reporting.

Fiscal Year 2020-2021 Active Grants
(Funding Year 2018-2019)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
9AZ02	Florida Atlantic University	Henrriette van Praa, PhD	$ 250,000	02/28/2023	No	Yes	No
9AZ31	University of South Florida	Joshua Gamsby, PhD	$ 237,500	03/31/2022	No	Yes	No

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

Principal Investigator: Henrriette van Praa, PhD

Organization: Florida Atlantic University

Abstract: 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. Physical exercise may slow disease progression and is a potentially modifiable risk-factor that may delay or prevent cognitive decline. Research has proven that running increases the production of new neurons in the hippocampus, a region important for learning and memory. Since this discovery, further research has demonstrated 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 (Aβ) production, reduces neuroinflammation, increases adult neurogenesis and benefits learning. 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. 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 (myokines) that circulate and communicate with the brain. The research team's studies indicate that myokines, can increase neural stem cell differentiation, and may be important for improvements in memory function in mice and humans. Research proposes 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, 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 APPswe/PS1Δ9 transgenic mice. Research further evaluates adult hippocampal neurogenesis, Brain-Derived Neurotrophic Factor (BDNF) levels and synaptic plasticity after these manipulations. The mouse behavioral experiments are in progress. In particular, evaluating spatial memory function and pattern separation behaviors. In addition, viral vectors and performed stereotaxic surgeries have been conducted to target newly born neurons in the hippocampus of AD mice housed under control and running conditions, and analyzing the fine morphology of adult-born neurons. The research will also assay Aβ and tau levels in the hippocampi and cortices of these subjects and aim to discover novel myokines that may aid brain function. The research will compare the effects of conditioned media secreted by 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 factors will be studied for their effects on neurogenesis and neurotrophin levels. These studies will add significantly to the understanding of the role of molecules secreted by skeletal muscle cells that translate exercise to improved brain function, providing important preclinical evidence for novel therapeutic strategies based on myokines that could benefit AD patients

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

Collaborations: None at the time of reporting.

Journals: Gaitan J.M., Moon H.Y., Stremlau M., Dubal D.B., Cook D.B., Okonkwo O.C., van Praag H. Effects of Aerobic Exercise Training on Systemic Biomarkers and Cognition in Late Middle-Aged Adults at Risk for Alzheimer's Disease. Front. Endocrinol. 12:660181. doi: 10.3389/fendo.2021.660181. 2021

Patents: None at the time of reporting.

2. **Grant #:** 9AZ31 Investigation of Alzheimer's Disease-induced Circadian Dysfunction on Tau Production and Phosphorylation

Principal Investigator: Joshua Gamsby, PhD

Organization: University of South Florida

Abstract: Over the past year, the Research team has made solid progress on aims despite many interruptions due to the global pandemic, such as the closing of the project lab for several weeks. First, it has been determined that tauopathy, a hallmark pathology associated with Alzheimer's disease (AD), appears to impact the circadian clock only mildly. This suggests a more prominent role for beta amyloidosis, another AD hallmark pathology. Secondly, the research confirms that Microtubule Associated Protein Tau (MAPT), the gene responsible causing tauopathy, is a clock-controlled gene. This suggests that disruptions of normal circadian rhythmicity, such as chronic jet lag, might disrupt MAPT transcription leading to an increased susceptibility of tauopathies such as AD. Additionally, the Research team has published five papers, and has submitted one R21 grant application to the NIH that will be expanded R01 proposal this upcoming spring. It should also be mentioned that this grant has created two technician jobs and numerous purchases to support these experiments contribute to the Florida economy.

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

Collaborations: As a result of this research grant, collaborations with the Hurely lab from RPI, the Lee lab at the University of Kentucky, and the Gulick lab at USF have been developed. Additiona collaboration with Dr. Arunava Roy, was established to help with ChIP assay.

Journals: Sandusky-Beltran LA, Kovalenko A, Placides DS, Ratnasamy K, Ma C, Hunt JB, Jr., Liang H, Calahatian JIT, Michalski C, Fahnestock M, Blair LJ, Darling AL, Baker JD, Fontaine SN, Dickey CA, Gamsby JJ, Nash KR, Abner E, Selenica MB, Lee DC. Aberrant AZIN2 and polyamine metabolism precipitates tau neuropathology. J Clin Invest. 2021;131(4). Epub 2021/02/16. doi: 10.1172/JCI126299. PubMed PMID: 33586680; PMCID: PMC7880423.

Mahoney H, Peterson E, Justin H, Gonzalez D, Cardona C, Stevanovic K, Faulkner J, Yunus A, Portugues A, Henriksen A, Burns C, McNeill C, Gamsby J, Gulick D. Inhibition of casein kinase 1 delta/epsilon improves cognitive performance in adult C57BL/6J mice. Sci Rep. 2021;11(1):4746. Epub 2021/02/28. doi: 10.1038/s41598-021-83957-9. PubMed PMID: 33637777; PMCID: PMC7910436.

Carter B, Justin HS, Gulick D, Gamsby JJ. The Molecular Clock and Neurodegenerative Disease: A Stressful Time. Front Mol Biosci. 2021;8:644747. Epub 2021/04/24. doi: 10.3389/fmolb.2021.644747. PubMed PMID: 33889597; PMCID: PMC8056266.

Araujo I, Henriksen A, Gamsby J, Gulick D. Impact of Alcohol Abuse on Susceptibility to Rare Neurodegenerative Diseases. Front Mol Biosci. 2021;8:643273. Epub 2021/06/29. doi: 10.3389/fmolb.2021.643273. PubMed PMID: 34179073; PMCID: PMC8220155.

Beesley S, Kim DW, D'Alessandro M, Jin Y, Lee K, Joo H, Young Y, Tomko RJ, Jr., Faulkner J, Gamsby J, Kim JK, Lee C. Wake-sleep cycles are severely disrupted by diseases affecting cytoplasmic homeostasis. Proc Natl Acad Sci U S A. 2020;117(45):28402-11. Epub 2020/10/28. doi: 10.1073/pnas.2003524117. PubMed PMID: 33106420; PMCID: PMC7668169

Patents: None at the time of reporting.

Fiscal Year 2020-2021 Active Grants
(Funding Year 2017-2018)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
8AZ04	Florida International University	Madhavan Nair, PhD	$ 224,643	02/28/2022	No	Yes	Yes
8AZ12	The University of Central Florida Board of Trustees	Kenneth Teter, PhD	$ 200,000	02/28/2022	No	No	No
8AZ16	The University of Florida	Paramita Chakrabarty, PhD	$ 221,000	02/28/2022	No	No	No
8AZ24	University of Miami	Michal Toborek, MD, PhD	$ 221,000	02/28/2022	No	Yes	No
8AZ30	University of South Florida	Paula C. Bickford, PhD	$ 200,000	02/28/2022	No	No	No

1. **Grant #:** 8AZ04 Therapeutic Role of Withaferin A and Cytokine Release Inhibitory Drug-3 in the Prevention of Alzheimer's Disease, a Novel Nanotechnology Approach

Principal Investigator: Madhavan Nair, PhD

Organization: Florida International University

Abstract: Alzheimer's disease (AD) is a growing global threat to healthcare in the aging population, currently one in nine persons over the age of 65 years live with AD in United States (US). The pathology is marked by the accumulation of amyloid-beta (Aβ) deposition in the brain, which is further enhanced by the neuroinflammatory process. Nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3 (NLRP3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) are the major neuroinflammatory pathways that intensify AD pathogenesis. Histone deacetylase 2 (HDAC2)-mediated epigenetic mechanisms play a major role in the genesis and neuropathology of AD. Therefore, therapeutic drugs, which can target Aβ production, NLRP3 activation, and HDAC2 levels, may play a major role in reducing Aβ levels and the prevention of associated neuropathology of AD. In this study, we demonstrate that Withaferin A (WA), an extract from Withania somnifera plant, significantly inhibits the Aβ production and NF-κB associated neuroinflammatory molecules' gene expression. Furthermore, we demonstrate that cytokine release inhibitory drug 3 (CRID3), an inhibitor of NLRP3, significantly prevents inflammasome-mediated gene expression in our *in vitro* AD model system. Previously we have demonstrated that mithamycin (HDAC2 inhibitor) , alcohol, HIV neurotoxin Tat and cocaine upregulated the production of Aβ secretion in SHAPP cells and WA significantly suppressed the Aβ40 production.

Florida International University has further studied the impact of inflammatory markers in SHAPP cells and found CRID3 at 1 μM concentration reduced the IL-1α significantly, while WA had minimal effect. Researchers did not observe significant changes in the IL-1β under the same conditions. We have also studied effects on Caspase 1, an enzyme which activates pro inflammatory cytokines such as IL-1β. Our results showed reduction in Caspase-1 activation with use of CRID3 and WA combination in an *in vitro* combination model using neuronal SHAPP cells and microglial HMC-3 cells.

Further, to address the issue of minimal drug bioavailability in the brain due to the inability of free drugs crossing the Blood Brain Barrier (BBB), the research team developed the various nanoformulations (NFs) containing WA, CRID3 and MENPs in different combinations. WA loaded liposomal nanoformulation (WA-LNF) was characterized for size (499+/-50nm), toxicity and drug binding efficacy (28%). Our *in-vitro* BBB transmigration studies demonstrated 40% transmigration of WA-LNF. Complete NF, containing WA, and CRID3 bound MENPs, were made, and found that these LNFs were 183.7 nm in size, and the binding efficacy was 85% for WA and 16% for CRID3. The impact on various cytokines were analyzed using a neuronal and microglia cell culture model, where cells were exposed to different concentrations of WA (1μM; 2μM); CRID3 (1 μM) and complete NF (MENP-CRID3-Liposome-WA). After 24h, supernatant was assayed using Human Cytokine Array and five cytokines showed significant variations, namely, MIF, SERPINE1, IL-6, IL-8, and CXCL1. These cytokines known to be involved in AD progression and neurodegeneration. Reduction of these inflammatory pathways is a promising attempt to tackle the effects of Aβ plaques and Alzheimer's disease-associated neurodegeneration.

Follow-on Funding: Effect of a potent and metabolically stable endocannabinoid receptor agonist on inflammasome-induced neuroinflammation in a comorbid mouse model of Alzheimer's disease and HIV. National Institute on Drug Abuse. Nair. $364,202.

Collaborations: None at the time of reporting.

Journals: Kolishetti, N.; Vashist, A.; Arias, A. Y.; Atluri, S.; Dhar, S.; and, Nair, M. "Recent advances, status, and opportunities of magneto-electric nanocarriers for biomedical applications" Mol. Asp. Med., 2021, 101046. (https://doi.org/10.1016/j.mam.2021.101046); PMID:34743901.

Patents: None at the time of reporting.

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

Principal Investigator: Kenneth Teter, PhD

Organization: The University of Central Florida Board of Trustees

Abstract: The University proposed that Protein Disulfide Isomerase (PDI) can act as a disaggregase to dissolve and detoxify aggregated fibrils of the Aβ peptide. Thus, recombinant PDI could be used as a novel therapeutic agent for the clearance of extracellular Aβ fibrils that contribute to Alzheimer's Disease (AD). The board will pursue this possibility by identifying the minimal PDI fragment with disaggregase activity and the molecular mechanism for its neuroprotective function.

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. Researchers 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 Aβ aggregate. This provides a mechanical force to break apart nascent aggregates of Aβ. In the context of this model, we purified a panel of PDI deletion constructs

and established a number of techniques to evaluate the interactions between Aβ and specific domains of PDI. Binding assays have shown PDI does not interact with monomeric Aβ, which means the inhibitory effect of PDI on Aβ aggregation occurs after the onset of aggregation. This suggests PDI recognizes early, oligomeric aggregates of Aβ and may act as a disaggregase for this form of Aβ. We will soon examine this possibility with two newly developed assays that can distinguish oligomeric from monomeric Aβ: addition of PDI or certain PDI deletion constructs should revert oligomeric Aβ to its monomeric form. Another assay has been developed to document the structural changes in PDI that accompany its binding to aggregated Aβ. This assay has detected the unfolding of PDI that occurs when it binds to Aβ. Its future use will allow us to determine which domain(s) of PDI unfold upon contact with Aβ. Progress during the 2020-2021 reporting period was hampered by COVID-19 and the presence of aggregated Aβ in our recently purchased stocks of monomeric Aβ. Many of the newly developed assays can be performed in high-throughput fashion and should lead to rapid advances once we validate the monomeric nature of our new Aβ stock.

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.

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

Principal Investigator: Paramita Chakrabarty, PhD

Organization: The University of Florida

Abstract: The University of FLorida have conducted research to understand the biological mechanisms underlying ABI gene family member 3 (Abi3) and 1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-2 (Plcg2) mediated events that alter microglia function and Alzheimer's pathogenesis. These two gene variants are involved in Alzheimer's disease risk: Abi3 increases risk while Plcg2 lowers risk. Together the team has successfully completed the research on Abi3 mouse model which shows that the disease related Abi3 gene variant is putatively a loss of function mutation. This is very important for the field as our data also shows that glial activation can have beneficial effects on amyloid deposition in the early disease phase. Researchers also show that glial activation can have a detrimental effect on tau. This requires us to have a cautious approach when using immune therapies in patients because such therapies would have to be tailored to the neuropathological staging (amyloid and tau) of the patient. The team has also requested a no cost extension for our project. This will facilitate our successful completion of the project, publication of the manuscripts that have been submitted and also generate data that we can use to get additional grants. Due to the COVID-19 related closures, the University was unable to do any wet bench experiments (immunohistochemistry of brain slides, setting up cell culture experiments, etc) in 2020 for six months. Several technicians also left the lab and because of hiring freeze, scientists were unable to hire additional employees until spring 2021. This has resulted in some delays and thus the no cost extension will be helpful.

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

Collaborations: The University of Florida has set up several collaborations during this reporting period: Dr. Malu Tansey to work on Plcg2 mice (University of Florida); Dr. Stefan Prokop: collaboration on RNAscope on Abi3 KO mice (University of Florida); Dr. Nilufer Taner: collaboration to use NIA AMP AD data to support Abi3 KO mouse manuscript (Mayo Clinic Jacksonville)

Journals: None at the time of reporting.

Patents: None at the time of reporting.

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

Principal Investigator: Michal Toborek, MD, PhD

Organization: University of Miami

Abstract: 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 (EVs), carry content characteristic to the cells they originate from, including a protein called amyloid beta (Aβ). Deposits of Aβ in the brain have been linked to the memory loss and cognitive decline in individuals suffering from Alzheimer's Disease (AD). The mechanistic link between elevated deposits of Aβ in the brain and loss of memory in AD is not fully understood. Our project is based on the hypothesis that ECVs carrying Aβ can deliver this cargo to Neural Progenitor Cells (NPC), cells that produce new neurons even in the adult brain. NPC-derived neurons are critically important for normal brain function because they are built into normal neuronal networks and participate in memory formation.

Work on the project progresses as planned. During the reporting period, the majority of the work focused on advanced proteomic studies to identify protein cargo carried by EVs. The research team's proteomic analyses identified several unique protein-protein interactions as possible new targets to deliver Aβ to distant cells and tissues via EVs. The team explored functional outcomes of such protein-protein interactions. One main hub was Serpine-1 (plasminogen activator inhibitor 1). Serpine-1 is considered a major player in Aβ pathology as knock out (KO) of Serpine-1 gene or inhibition of Serpine-1 decreased Aβ burden in AD transgenic mice. In spite of that, the role of EV-associated Serpine-1 in amyloid pathology was not well studied. Serpine-1 was shown to be present in microparticles/platelets in the blood but there are no publications regarding EV-Serpine-1 in HIV-associated Aβ pathology. It is hypothesized that EV-associated Serpine-1 could be a main player of the EV-mediated Aβ pathology.

The team confirmed the proteomic results by measuring Serpine-1 level and activity in EVs. Unexpectedly, Serpine-1 protein levels were much higher in isolated EVs as compared to the parent cells, indicating a preferential transfer to EVs. Next, it was evaluated if Serpine-1 can be transferred via HBMEC-EVs to neural progenitor cells. Neural progenitor cells are the cell population that matures into neurons and contributes to learning and memory processes. As presented in our previous progress reports, differentiation of neural progenitor cells into mature neurons was diminished upon treatment with EV-Aβ. Thus, it was very important to show elevated levels of Serpine-1 in neuronal progenitor cells exposed to EV isolated from Human Brain Microvascular Endothelial Cells (HBMEC) treated with Aβ and/or HIV. In addition,

Serpine-1 levels were increased in cell culture media of neural progenitor cells. Finally, enzymatic activity of Serpine-1 measure as tissue plasminogen activator (tPA) was elevated. The team is now focusing on biological significance of this process in neural progenitor cell differentiation. The team also identified that the same EVs that carry Aβ can also transfer Serpine-1 as their cargo. It is believed that these are remarkable observations and we plan to continue this line of investigations.

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

Collaborations: Dr. Marta Garcia Contreras from the Diabetes Research Institute at the University of Miami School of Medicine on analysis of extracellular vesicles, with Dr. Shanta Dhar from the Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Dr. Daniel Adesse from the Instituto Oswaldo Cruz, Fiocruz, Brazil, and Dr. Joice Stipursky from the Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Brazil.

Journals: Cho HJ, Velichkovska M, Schurhoff N, András IE, Toborek M. Extracellular vesicles regulate gap junction-mediated intercellular communication and HIV-1 infection of human neural progenitor cells. Neurobiol Dis Neurobiol Dis. 2021 Jul;155:105388. doi: 10.1016/j.nbd.2021.105388.

Patents: None at the time of reporting.

5. **Grant #:** 8AZ30 Exploiting GPRC6a Antagonist to Mitigate Tau Deposition

Principal Investigator: Paula C. Bickford, PhD

Organization: University of South Florida

Abstract: One major hallmark of Alzheimer's Disease (AD) includes tau neuropathology and encompasses number more than 15 neurodegenerative diseases collectively known as tauopathies. Strategies aimed at reducing tau burden include increasing clearance, reducing aggregation, and modifying inflammation. Our group uncovered a unique interaction between the arginine metabolism and tauopathies. Arginine metabolism affects multiple biological processes that show considerable influence upon tau biology. We show that Arg1 reduces many aspects of the tau phenotype (hallmarks comprised of tau effects) and posit that the depletion of arginine increases autophagy through amino acid sensing. G-protein coupled receptor 6a (GPRC6a) is a G-protein coupled receptor recently shown to bind arginine affinity. Although, it remains unclear to the exact role of GPRC6a, we postulate that GPRC6a associates with autophagy. Our central hypothesis states that decreased signaling of GPRC6a activates autophagy and tau clearance. GPRC6a remains tonically activate and senses extracellular amino acid abundance arginine during neurodegenerative conditions. Utilizing a novel allosteric antagonist to GPRC6a, we found clearance of tau in primary neurons, overexpressing tau cells and P301S tau transgenic mice. Herein, we will elucidate a mechanism by which GPRC6a modifies tau metabolism using several approaches: genetic repression via gene therapy of GPRC6a and novel allosteric antagonists to GPRC6a. It will be determined whether genetically and pharmacologically repression of GPRC6a impacts tau deposition in mice. We will test if central administration of GPRC6a antagonists promotes tau clearance mice. Validation of our hypothesis will aid in our understanding of arginine-sensing mammalian target of rapamycin

(mTORC1) regulation during tauopathies and provide new targets for AD. The potential discovery of a "new class" of agents that modulate regulate autophagy could offer new therapeutics in the clinic for this devastating disease. The University of South Florida analyzed western blot analyses from brains of mice injected with short hairpin ribonucleic acid (shRNA)-scrambled control and shRNA-GPRC6a and analyzed western blot analyses from brains of non-transgenic and tau P301S (PS19) mice injected with either recombinant adeno associated virus rAAV shRNA-scrambled control and shRNA-GPRC6a. Regarding experimental design, mice were injected with either viral construct at four months of age and allowed to incubate for a duration of four months. Mice were euthanized at approximately nine months following the behavioral battery. Mouse brains were extracted and dissected into different regions on ice and frozen until further analysis.

The team also measured the three different fractions of brain lysate including a soluble fraction, detergent soluble (sarkosyl soluble) and detergent insoluble (sarkosyl insoluble) for phospho tau. These data indicate that shRNA GPRC6a reduces certain pools of tau particularly highly insoluble tau species including total tau and phospho tau.

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 2020-2021 Closed Grants
(Funding Year 2020-2021)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
21A02	Florida Atlantic University	Alex C. Keene, PhD	$ 198,097	02/28/203	No	No	No

1. **Grant #:** 21A02 (Relinquished) The Cellular Basis for Neurodegeneration in a Drosophila Model of Alzheimer's Disease

Principal Investigator: Alex C. Keene, PhD

Organization: Florida Atlantic University

Abstract: Staff completed analysis of the effects of aging and Alzheimer's variants on proboscis extension reflex in flies and identified that Alzheimer's Disease (AD) variants recapitulate early aging. Surprisingly, there is little effect of these variants on synaptic structure, suggesting changes in neural function, rather than structure are impacting the taste system. The team is currently writing these findings up for publication. The postdoc associated with the grant (Liz Brown) received a K99 award. Staff were disappointed in the decision to terminate the grant, after arrangements for the principal investigator to retain a part-time faculty position were proceeding favorably. Because of this, staff were no longer able to fund the graduate student associated with the award (Justin Palermo) and he has transferred from FAU's graduate program to Texas A&M where he will finish his degree. Future plans include developing any new scientific directions and/or taking advantage of new research opportunities/follow-on funding. The team plans to submit an R01 building off this work once the TRAP- seq is included. In addition, the team is proud that Liz Brown is in the NIH's first class of K99-MOSAIC fellows and will continue to support her work.

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.

Fiscal Year 2020-2021 Closed Grants
(Funding Year 2019-2020)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
20A03	Florida Atlantic University	Maria Ordonez, DNP, APRN	$100,000	10/31/2021	No	No	No
20A07	Florida Atlantic University	Pamela J. McLean, PhD	$99,000	04/30/2020	No	No	No

1. **Grant #:** 20A03 Opening and Sustaining Loving, Caring Conversations on Advance Care Planning for Patients and Families Living with Alzheimer's Disease

Principal Investigator: Maria Ordonez, DNP, APRN

Organization: Florida Atlantic University

Abstract: Florida Atlantic University's Louis and Anne Green Memory and Wellness Center (MWC), Charles E. Schmidt College of Medicine, and Office of Interprofessional Education created an interprofessional team of researchers to study Advance Care Planning (ACP). The project, *Opening and Sustaining Loving, Caring Conversations on Advance Care Planning for Patients and Families Living with Alzheimer's Disease,* focuses on conducting timely, meaningful conversations and education about ACP with persons living with Alzheimer's Disease (AD) and their families. The team wants to simplify current, unclear, negative language in ACP documents and processes to easily understood terminology that expresses comfort, love, and caring. The team will address a gap in the existing language as there are no statutory United States (US) state advance directives that specifically address AD, the sixth leading cause of death in US, as a condition to optimize the level of care. Goal is promotion and best practices for conducting ACP in persons and families living with AD using all available tools. The team will create a simple ACP toolkit to be utilized at the MWC and further promote ACP discussion and completion through primary care services and community healthcare specialties by developing a brief train the trainer program. The MWC houses a state designated Memory Disorder Clinic (MDC) under Florida Department of Elder Affairs (DOEA) Alzheimer's Disease Initiative and an Adult Day Center licensed by the Agency for Health Care Administration designated as Specialized Alzheimer's Service Center. The MWC is ideally positioned as practice site and pillar for the proposed project. It provides an array of dementia specialized programs of care and supportive services for persons living with or at risk for AD or Related Dementias (ADRD) and their families. Currently, 29.5% of new patients seen at the MWC have completed ACP, which aligns with national averages. The MWC actively collaborates with a statewide network of 17 MDCs and participates in other DOEA programs and advocacy.

One of the major goals for the project was to learn about existing barriers that Floridians living with AD experience that prohibit them from completing Advance Care Planning (ACP). So far, we have been able to initially learn about some of these barriers through the literature, through first-hand experiences with our Interprofessional Advisory Group members, and through the creation of an initial ACP Toolkit and the difficulties of developing a simple document that is not "one-size-fits-all." The three goals of our project are to develop an ACP Toolkit simplifying language of advance care planning to share with persons living with AD and their families and caregivers, develop a Train-the-Trainer (T-T) program to educate community healthcare providers (we are behind on the T-T due to COVID-19), and create a plan to assess parts one

and two. We have not been able at this point to assess plans for parts one and two due to COVID-19 university and center adjusted protocols. Nevertheless, we are determined and on target for the end of this pilot project, as we will be able to increase the number of ACPs, thereby reducing the cost of AD by minimizing unwanted care.

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 #:** 20A07 Modeling Lewy Body Dementias: Towards a Better Understanding of Amyloid-Beta and Alpha-Synuclein in ADRDs

Principal Investigator: Pamela J. McLean, PhD

Organization: Mayo Clinic

Abstract: Lewy Body Dementia (LBD) research suffers from a lack of convincing and relevant animal models to elucidate the molecular characteristics and consequences of comorbid amyloid-beta (Aβ) and alpha-synuclein (αsyn) pathologies. Development of better models recapitulating the comorbid pathology and differential clinical presentation of LBD will help better understand the pathogenesis and cellular mechanisms that lead to these disorders. In this pilot project scientists proposed to investigate if Aβ and αsyn work synergistically to influence disease pathogenesis by conditionally inducing the hallmark co-pathologies in adult mice. To determine if αsyn and Aβ crosstalk results in accelerated and enhanced pathology and behavioral dysfunction in an existing transgenic mouse model, researchers used adeno-associated virus (AAV-PhP.eB) to induce widespread αsyn expression in the adult brain of APP/PS1 transgenic mice. During the course of this pilot project, researchers developed and optimized the use of AAV-PhP.eB to transduce adult mouse brain via tail-vein injection. The team established a colony of APP/PS1 transgenic mice to generate the numbers of animals required for our experimental paradigm. Initially, researchers experienced some problems establishing the colony as the mice were failing to breed or litters were not surviving. Eventually the team established successful breeding conditions to generate mice for AAV transduction. After successfully establishing the experimental paradigm researchers injected a cohort of APP/PS1 transgenic mice and littermate controls aged to three months with either control AAV-PhP.eB-Venus-YFP or experimental AAV-PhP.eB-synuclein which represented our pre-amyloid-beta pathology cohort (Group 1 & 2). Unfortunately, several animals were lost to attrition; in particular transgenic APP/PS1 mice transduced with WT synuclein died before the endpoint which resulted in significantly smaller group sizes and a lack of power for statistical comparisons. Scientists performed behavioral analyses as described in experiment one which included a battery of tests and report the data below. Researchers did not detect any statistically significant differences between the groups however as noted above, Researchers lost seven mice during the study which significantly decreased the size of each group and precluded our ability to draw any conclusions from the behavioral analyses. Additional experiments, including immunohistochemistry, protein ligation assay, and biochemical analyses were not completed within the time-frame of the current funding due to the delays in establishing the colony

however, these experiments will be continued and completed outside this funding period. In addition, due to the unexpected death of virally transduced animals the team made the decision not to inject a six-month-old cohort of APP/PS1 mice and halted the study after just one cohort.

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.

Fiscal Year 2020-2021 Closed Grants
(Funding Year 2018-2019)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
9AZ01	Florida Atlantic University	Monica Roselli, PhD	$235,019	09/30/2021	No	Yes	No
9AZ03	Florida Atlantic University	Ruth M. Tappen, EdD, RN, FAAN	$250,000	04/30/2021	No	No	No
9AZ05	Florida Atlantic University	Behnaz Ghoraani, PhD	$94,709	02/28/2021	No	Yes	No
9AZ06	Florida Atlantic University	Jianning Wei, PhD	$95,000	08/31/2021	No	Yes	Yes
9AZ07	Florida International University	Shanna L. Burke, PhD, MSW, MPH	$94,999	02/28/2021	No	Yes	Yes
9AZ08	Mayo Clinic Jacksonville	Mark T.W. Ebbert, PhD	$237,500	02/28/2022	No	No	No
9AZ09	Mayo Clinic Jacksonville	Yonghe Li, PhD	$95,000	02/28/2021	No	No	No
9AZ11	Mount Sinai Medical Center	Maria Greig-Custo, MD	$234,500	03/31/2021	No	No	Yes
9AZ12	University of Central Florida	Tracy C. Wharton, PhD, MSc, MEd, MSW, LCSW, QCS	$94,999	02/28/2021	No	No	No
9AZ13	University of Florida	Cynthia Garvan, PhD	$95,000	08/31/2021	No	No	No
9AZ14	University of Florida	Demetrius M. Maraganore, MD	$237,500	02/28/2021	No	No	No
9AZ15	University of Florida	Glen Smith, PhD	$237,500	08/31/2021	No	Yes	Yes
9AZ16	University of Florida	Gordon Mitchell, PhD	$237,498	02/28/2021	No	No	No
9AZ17	University of Florida	Benoit Giasson, PhD	$237,500	03/28/2021	No	Yes	No
9AZ18	University of Florida	Neal Jeffrey Weisbrod, MD	$87,182	08/31/2021	No	No	No
9AZ19	University of Florida	Catherine Price, PhD	$237,080	09/30/2021	No	No	Yes
9AZ20	University of Miami	Varan Govind, PhD	$87,182	02/28/2021	No	No	No
9AZ21	University of Miami	Rosie E. Curiel Cid, PsyD	$84,301	08/31/2020	No	Yes	Yes
9AZ22	University of Miami	Philip Harvey, PhD	$87,830	08/31/2020	No	Yes	No
9AZ23	University of Miami	Scott C. Brown, PhD	$95,000	02/28/2021	No	Yes	No
9AZ24	University of Miami	David Lowenstein, PhD.	$237,171	8/31/221	No	No	No
9AZ25	University of Miami	Tatjana Rundek, MD, PhD	$237,500	02/28/2021	No	Yes	Yes
9AZ26	University of South Florida	Debra Dobbs, PhD	$249,996	02/28/2021	No	No	No
9AZ27	University of Central Florida	Kyaien O. Conner, PhD, LSW, PMH	$95,000	08/31/2021	No	No	No
9AZ28	University of South Florida	Hongdao Meng, PMH, PhD	$94,860	02/28/2021	Yes	No	No
9AZ29	University of South Florida	J. Matt Webster, PhD	$95,000	08/31/2021	Yes	No	No
9AZ30	University of West Florida	Crystal Bennett, PhD, RM	$34,992	08/31/2021	Yes	Yes	Yes

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 Roselli, PhD

Organization: Florida Atlantic University

Abstract: This research project examined the association between bilingualism, Executive

Function (EF), and brain volume in older monolinguals and bilinguals who spoke English, Spanish, or both, and were diagnosed as Cognitively Normal (CN), with Mild Cognitive Impairment (MCI), or with dementia. Increased Gray Matter Volumes (GMV) were found in language and EF brain regions among bilinguals, but there were no differences in memory regions between bilinguals and monolinguals. Neuropsychological performance did not vary across language groups over time; however, bilinguals exhibited reduced Stroop interference and lower scores on Digit Span Backwards and category fluency. Higher scores on Digit Span Backwards were associated with a younger age of English acquisition, and a greater degree of balanced bilingualism was associated with lower scores on category fluency. The initial age of cognitive decline did not differ between language groups. The influence of bilingualism appears to be reflected in higher GMV within language and EF regions, and to a lesser degree, in performance on tasks measuring EF.

The research team examined the extent to which bilingualism was associated with the integrity of white matter interhemispheric tracts in cognitively normal elderly adults compared to those with cognitively atypical aging (MCI and dementia). Results showed that bilinguals have larger anterior corpus callosum, but smaller intercallosal temporal lobe tracts compared to monolinguals. These results suggest that the size of white matter is susceptible to the effects of language experience.

Florida Atlantic University, University of Florida, and Mount Sinai Medical Center have assisted in collecting, analyzing, and authoring this research. Unfortunately, due to the spread of the COVID-19 pandemic and the resulting closures and lockdowns, the progress of this research was impacted significantly because participants are in the age group of 65 and older, and this population is vulnerable to the detrimental effects of COVID-19.

Follow-on Funding: Postdoctoral Research Fellowship in Neuropsychology and Brain Biomarkers of Abnormal; FDOH Grant Mechanism: Fellowship;Monica Rosselli; $99,051.

Collaborations: None at the time of reporting.

Journals: Bilingualism: Language and Cognition. Valeria L. Torres, Mónica Rosselli, David A. Loewenstein, Merike Lang, Idaly Vélez-Uribe, Fernanda Arruda, Joshua Conniff, Rosie E. Curiel, Maria, T. Greig, Warren W. Barker, Miriam Rodriguez, Malek Adjouadi, David E. Vaillancourt, Russell Bauer, and Ranjan Duara. The Contribution of Bilingualism to Cognitive Functioning and Regional Brain Volume in Normal and Abnormal Aging. 2021.

Patents: None at the time of reporting.

Patents: None at the time of reporting.

2. **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: Driving cessation has a profound effect on functional independence, self-esteem, mood, social life and ability to obtain needed services. Powerful emotions may be unleashed

when the individual is told to stop driving. Families report this is one of the most difficult decisions they encounter in caring for a person with dementia. In addition, providers report considerable uncertainty about assessing and reporting fitness to drive, an uncertainty supported by low agreement between physician assessment and on-road driving evaluation. Objective evidence of the risk in continuing to drive is clearly needed. The proposed Fit2Drive Calculator is an innovative, evidence-based system for predicting the likelihood of passing an on-road driving evaluation developed for individuals with cognitive concerns, mild cognitive impairment (MCI) or early stages Alzheimer's disease. It is based on a prototype we developed from driving registry data at our Memory and Wellness Center. Results of two brief tests, the MMSE and Trails B time, yielded a 75% accurate prediction of passing an on-road evaluation but it is limited by the paucity of unimpaired individuals and a non-diverse sample. To address these limitations and produce a more sensitive and specific predictor, we propose recruiting a more diverse sample of community-based older adults age 65 with a MoCA score of 19 who will take a battery of brief tests of general cognition, executive function and a standard on-road driving evaluation designed specifically for this population. The results will be used to create a parsimonious algorithm for predicting likelihood of passing the lengthier and far more costly on-road evaluation. The algorithm will be incorporated into an app available on laptop or mobile device via the Fit2Drive website. Once the Fit2Drive Calculator has been improved and rigorously tested, further work would involve translation into clinical practice, dissemination andpotential development of an online self-test version.

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.

3. **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: We extracted gait data from 32 healthy, 26 mild conginitive impairment (MCI), and 20 Alzheimer's Disease (AD) participants collected using a computerized walkway. We used the gait characteristics and developed a machine learning algorithm to identify healthy vs. MCI vs. AD subjects using only their gait data. The researcher published this work in one conference paper and one journal paper. The conference paper was presented virtually in July 2020.

The research team designed a study and collected new data from 31 subjects (22 healthy, 6 MCI, and 3 AD/LBD). The data included wearable sensors movement data collected concurrently as the subjects walked on the computerized walkway. The team developed algorithms to extract the same gait characteristics as the computerized walkway from the wearable sensors data. We are now in the process of finalizing our analysis and writing a paper. The plan is to integrate our novel biomarkers obtained from this pilot project with balance, flexibility, and strength biomarkers into a combined score corresponding to clinical score of healthy, MCI, and AD. It is expected that the application of machine learning classifiers on the

combined comprehensive dual-tasking gait features and the assessments of balance, flexibility, and strength will further improve our models and enable detecting early-stage cognitive impairment.

Follow-on Funding: Advanced data analytics for early detection of Alzheimer's disease using wearables and smartphone; National Science Foundation; Behnaz Ghoraani; $524,000.

Collaborations: None at the time of reporting.

Journals: Dual-Task Gait Assessment and Machine Learning for Early-Detection of Cognitive Decline. Boettcher, L.N., Hssayeni, M., Rosenfeld, A., Tolea, M.I., Galvin, J.E., and Ghoraani, B. Proceedings of the IEEE Engineering in Medicine and Biology Society. 2020.

Detection of Mild Cognitive Impairment and Alzheimer's Disease Using Dual-Task Gait Assessments and Machine Learning, Ghoraani, Boettcher, L.N., Hssayeni, M., Rosenfeld, A., Tolea, M.I., Galvin, J.E. Journal of Biomedical Signal Processing and Control. 2020.

Patents: None at the time of reporting.

4. **Grant #:** 9AZ06 Effect of Neuronal Activity of Synaptopathy in Alzheimer's Disease Using a Novel Multi- Electrode Microfluidic Platform

Principal Investigator: Jianning Wei, PhD

Organization: Florida Atlantic University

Abstract: In this pilot grant, we propose to use a novel microfluidic platform to study how different patterns of neuronal activity (physiological vs. repeated stimulation) contribute to Alzheimer's Disease (AD) synaptopathy. The research team optimized the microfluidic design with embedded electrodes and successfully cultured compartmentalized normal and AD neurons in these chambers. The team applied electrical and chemical stimulations to the neuronal culture and showed that different patterns of stimulation affected the production of beta-amyloid differently. The team investigated axonal mitochondria transport under different stimulations and extend the study to neurons differentiated from induced pluripotent stem cells (iPSCs) derived from healthy and AD patients. The team is currently establishing the protocol for iPSC maintenance and differentiation and has also established neuronal culture in multi-microelectrode arrays (MEA) chambers.

There are no significant changes in the key personnel, scientific programs, shared resources, and/or institutional commitments to report. The COVID-19 pandemic has greatly affected the research progress. The team could not fabricate the microelectrode embedded microfluidics that usually took place at University of Miami. Instead, the focus was on the chemical stimulation and electrical stimulation using MEA chambers.

It is planned to continue to investigate how neuronal activity affect synaptic protein homeostasis and synaptic functions. Also planned is to do the work using the iPSC-based neuronal model. With the data generated from this pilot grant, team wish to extend our research scope to investigate how different patterns of neuronal activity affect microglia behavior (migration and cytokine release profile, specifically) and therefore neuroinflammation. The patterns of neuronal activity will be selected based on this study. A co-culture of neurons and microglia differentiated

from iPSCs of healthy and AD patients will be seeded in the MEA chamber developed in this study. .

Follow-on Funding: Alzheimer's-focused administrative supplements for NIH grants that are not focused on Alzheimer's disease and PA-18-591; NIH/NIBIB; Jianning Wei, Erik Engeberg, Emmanuelle Tognoli, Sarah Du; $349,939.

Collaborations: New collaborations were established on MEA studies with Dr. Erik Engeberg from College of Engineering at Florida Atlantic University

Journals: An impedimetric assay for the identification of abnormal mitochondrial dynamics in living cells. Galpayage Dona, K., Du, E., Wei, J. Electrophoresis, 2021.

RNA-seq analysis reveals significant transcriptome changes in huntingtin-null human neuroblastoma cells. Bensalel J, Xu H, Lu ML, Capobianco E, Wei J., BMC Med. Genomics. 2021.

Impaired Restoration of Global Protein Synthesis Contributes to Increased Vulnerability to Acute ER Stress Recovery in Huntington's Disease. Xu H, Bensalel J, Capobianco E, Lu ML, Wei J. Cell Molecular Neurobiology. 2021.

Patents: None at the time of reporting.

5. **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, PhD, MSW, MPH

Organization: Florida International University

Abstract: The researchers will study the relationship between the presence of depression, anxiety, and sleep disturbance and changes in brain structure, examine the relationship between cognitive decline and brain changes, and identify biomarkers of disease severity and stage shared by both psychiatric conditions and Alzheimer's Disease (AD), while accounting for the gene, apolipoprotein e (APOE). Psychiatric conditions may increase the risk for AD, and changes in brain structures may be an indicator of these changes. The link between psychiatric conditions and AD and other dementias remains under study, but both cause changes in brain structure. This study is framed by three aims, which will organize our investigation of psychiatric conditions and associated subsequent neurodegeneration, such as AD, with a focus on the volumes of brain structures, which represent disease severity and stage. Florida International University (FIU) has submitted the manuscript based on the findings from aim 1 related to sleep and brain regions. FIU has been finalizing the aim 1 paper for publication submission specific to depression and the effects on brain regions. FIU has been finalizing the aim 1 results specific to anxiety and the effects on brain regions. FIU has delivered two posters and one oral presentation for the Gerontological Society of America, which was held virtually in November 2020. FIU has been preparing aim 3 analyses, including neuropatho/ogical outcomes. UF and FIU held internal team working meetings, respectively, UF has delivered the predicted outcomes that resulted from aim 2.

Follow-on Funding: Sleep and cognition among Latin midlife adults at-risk for Alzheimer's disease; Shanna L. Burke, PhD, Eric Wagner, PhD, Mariana Sanchez, PhD, Timothy Hayes; National Institute on Minority Health and Health Disparities; $359,653.74.

Collaborations: Florida International University is the lead University, in collaboration with University of Florida.

Journals: Burke, S., Grudzien, A, Li, T., Abril, M., Spadola, C., Barnes, C., Hanson, K., Grandner, M.A., & DeKosky, S. (Under Review). The Impact of Sleep Disturbance on Regional Brain Volumes. Submitted on 1/14/2021 to Sleep Medicine, ID #SLEEP-D-21-00046.

Patents: None at the time of reporting.

6. **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 Jacksonville

Abstract: Alzheimer's disease is complex and requires researchers to expand into new approaches to understand the underlying etiology. Large research efforts, including the International Genomics of Alzheimer's Project, have identified the top genes driving Alzheimer's disease status, and our group seeks to identify what is happening at the DNA and RNA levels within these top genes that drive disease development. We will perform deep, targeted long-read RNA isoform sequencing (IsoSeq) and long-read DNA sequencing in the lateral entorhinal cortex across Alzheimer's disease cases and controls, using PacBio long-read technology, to identify problematic RNA isoforms and structural DNA mutations. Our approach will enable us to identify disease-causing structural mutations and aberrant RNA isoforms driving both disease development and progression. Our approach provides a clear path to understanding a crucial aspect of Alzheimer's disease etiology by identifying structural mutations that may be the functional mutations associated with genome-wide association hits researchers have been looking for. By studying the lateral entorhinal cortex, where pathogenesis typically begins, we can maximize the likelihood of finding any mutations involved in disease, ultimately leading to effective therapeutics. It is critical that we study top genes in the diseased tissue. Dr. Ebbert has the required experience in Alzheimer's disease research, next-generation sequencing technologies, and advanced analysis techniques to carry out the aims outlined. We are confident existing evidence supports our aims and that this project will impact Alzheimer's disease research.

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

Understanding How Structural Mutations and Individual RNA Isoforms are Involved in Human Health and Disease. NIH/NIGMS. Mark Ebbert. $1,956,250.

Using Long-Range Technologies as a Multi-Omic Approach to Understand Alzheimer's Disease in Brain Tissue. NIH/NIA. Mark Ebbert. $3,096,700.

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

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

Principal Investigator: Yonghe Li, PhD

Organization: Mayo Clinic Jacksonville

Abstract: Wnt/β-catenin signaling is the key positive regulator of neuronal survival and adult neurogenesis in brain. Wnt/β- catenin signaling is greatly suppressed in Alzheimer's Disease (AD) brain, and the impaired Wnt/β-catenin signaling plays a critical role in AD pathogenesis. Therefore, we hypothesized that restoring Wnt/β-catenin signaling represents an opportunity for rational AD therapy. There are no disease-modifying treatments for AD. The current paradigms in AD drug discovery have shifted to the development of drugs that target multiple disease processes that link to the development and progression of AD. Wnt/β-catenin signaling is capable of orchestrating diverse events related to AD. As Wnt/β-catenin signaling pathway is diminished in AD brain, the research team hypothesized that restoring Wnt/β-catenin signaling represents an opportunity for rational AD therapy. In this project, by using iPSc-derived neurons and cerebral organoids and the 5xFAD mouse AD model, it was demonstrated that restoring Wnt/β-catenin signaling results in inhibition of Aβ production, tau phosphorylation and neuroinflammation, promotion of neurogenesis and synaptic plasticity, and alleviation of cognitive impairment. The findings provide the proof-of-concept that restoring Wnt/β-catenin signaling is a promising therapeutic strategy for AD therapy.

The current project, successfully demonstrated that restoring Wnt/β-catenin signaling alleviates cognitive impairment in the 5XFAD model of amyloid pathology. In the future, the project will further determine whether Wnt/β-catenin signaling alleviates neurodegeneration and cognitive impairment in the PS19 model of tauopathy.

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

Principal Investigator: Maria Greig-Custo, MD

Organization: Mount Sinai Medical Center

Abstract: The goal of the MindSight Training Program is to improve functional learning capacity and quality of life among patients with Mild Cognitive Impairment (MCI) and Early Stage Dementia and to compare results of the intervention through a Randomized control trial. The MindSight training program that incorporates a dyad approach (the cognitively impaired participant and a partner) is designed to be used in small groups in a classroom format. The proposed project is an extension of the MindSight Pilot Grant, 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 80 dyads from the Wien Center Clinic, and our Alzheimer's Disease Research Center which will be randomly allocated into: (1) a group that receives a combination of Mindfulness Training and Cognitive Exercises, versus (2) an Attention Control Group that engages in informal discussion of methods for cognitive enhancement and stress reduction. The outcome measures of the study will be a comprehensive test battery, questionnaires on well-being and quality of life, basic and instrumental Activities of Daily Living (ADLs), and salivary biomarkers of stress and inflammation (cortisol, alpha-amylase and CReactive Protein) that will be obtained at baseline, at six and 18 weeks. 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. The study partners will also benefit by improving their quality of life and through Mindfulness reduction stress strategies. 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.

Follow-on Funding: Impact of the MindSight Training Program versus Attention Control Training Program on Patients with MCI and Early Stage Dementia. FLDOH. Maria T. Greig Custa, MD. $237,500.

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

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

Principal Investigator: Tracy C. Wharton, PhD, MSc, MEd, MSW, LCSW, QCS

Organization: University of Central Florida

Abstract: The FL REACH translation project is a translational pilot study to test feasibility and effectiveness of a modified version of the evidence-based Resources for Enhancing Alzheimer's Caregiver Health (REACH) II clinical trial. The REACH II intervention is the gold-standard for evidence-based practices that address burden, well-being, and skills training. Few successful interventions have been translated into community based settings, and no translation has yet attempted to bridge psychosocial intervention and medical coordination of care using strengths-based and person centered approaches in an outpatient clinic setting. This study adapts critical components of REACH II: safety, caregiver well-being, skills development for Daily Living (DL)/Instrumental Activities of Daily Living (ADL)/behavior response, and includes material on care coordination, grief, and advanced care planning. The intervention will comprise four in person sessions and two phone sessions over six to eight weeks, delivered by a trained interventionist. There is a distinct benefit of providing intervention through the outpatient clinic. Although Florida is ethnically, racially, and linguistically diverse, there is disparity among families that engage with existing programs. In addition to racial/ethnic diversity, families who repeatedly return to the clinic in crisis tend to be less aware of resources that may be available and less inclined to use them. This pilot program engages a novel approach that provides

access to anyone who is diagnosed through the clinic, with a program that builds a bridge between the medical team and the psychosocial intervention, capitalizing on the rapport and trust that is built, and providing in-house opportunities to engage diverse populations with a program grounded in the evidence base. This intervention provides a foundational training for families that will bridge to seamless team coordination in the future. We will test feasibility and fidelity to the model, effectiveness of the intervention on key outcomes, and possible moderators of outcome, such as race/ethnicity, language, dosage, or relationship. Due to COVID-19-related social distancing requirements, program staff have re-structured the pilot to be conducted entirely by telehealth. This includes remote staff meetings, all sessions being conducted via telehealth, and study measurements being collected using online survey software. The project received rapid Institutional Review Board (IRB) approval to make the shift to continue without interruption for participants who were currently enrolled as of the closure of the clinics, and shortly after that were approved for using telehealth and survey software to do informed consent for new intakes to the program. There was a minor delay in new intakes, but the program was allowed to continue in the telehealth/online format. The program has continued to recruit new participants. This has been challenging, due to additional time needed by clinic staff to make additional phone calls, rather than a warm handoff in person, at a time when there are staffing restrictions. Clinic staff have been working hard to incorporate this into workflow, as they are also working remotely. As a result of these challenges, the program has recruited a steady number, although less than the original target for the pilot project. There are enough participants to complete the proposed analyses, however. Invitations have gone out for participation in the six month follow-up assessment and data are being collected for that assessment. Thirty-one people completed a baseline assessment; thirteen additional people were recruited and scheduled but never completed an intake to the program. Three people dropped out during the intervention, 9% attrition rate, twenty-eight participants completed a post-test assessment, data are being collected for six month follow up assessment, data are being collected for comparison group. Care recipient access to dangerous objects decreased (65.4% to 30.8%). Number of caregivers reporting three or more days of depressive symptoms per week reduced from 19.2% to 7.7%. Confidence in ability to use behavioral strategies in caregiving increased: At baseline, 23.1% were 'pretty confident' and none were 'very confident.' At completion, 80.7% were 'pretty' or 'very confident' (a 57.6% change). Satisfaction surveys indicate high satisfaction with all elements of the intervention, and comments from participants endorsed helpfulness and accessibility of this intervention. Comments included (copied verbatim from data collection):

"We are so glad that we were informed of this program. We would recommend this program to anyone dealing with a loved one suffering from alzheimers/dementia."

"I felt heard, understood and supported. My questions were always welcome and practical solutions were offered. Affirmation of my efforts to give care was so positive for me. I am thankful to have participated and even with the COVID-19 situation the program was available via zoom. I feel more able to keep on keeping on!"

"I'm hopeful the program will continue and will become the first step for any caregiver getting ready to take on care for loved ones."

"Program has been valuable as I had no knowledge of the disease prior to my spouse's diagnosis."

"It has been an honor to be a part of this program. I have engaged and learned so many helpful types and sources available to me. Keep up the good work!"

"FL REACH Program provided information that we use on a daily basis. We have a clear understanding of how to deal with our situation. Great program."

"Excellent program. Learned a lot. Folder with material is very good for reference and as needed. Thank you and God Bless you for this outstanding program."

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

Collaborations: University of Central Florida is the receiving institution for the grant. The graduate research assistant working as the project coordinator for this project assisted with data and telehealth materials preparation, and completed his term spring 2020.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

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

Principal Investigator: Cynthia Garvan, PhD

Organization: University of Florida

Abstract: With 1Florida ADRC (Alzheimer's Disease Research Center) data and measures of long term cortisol exposure obtained from hair of 1Florida ADRC participants, the team endeavors to validate findings in two recent studies which have shown a relationship between cortisol levels and stages of cognitive decline. Using imaging and cognitive assessment data from 1Florida ADRC participants. The team will correlate long term cortisol exposure with measures of brain integrity (e.g., amyloid-13 deposition, network connectively, free water, entorhinal thickness, leukoariosis). Additionally, we will correlate long term cortisol exposure with measures of executive function and memory. In this hypothesis generating aim, the team will explore the role of hypercorisolism in the pathogenesis and progression of AD. Using National Institutes of Health guidelines on conducting pilot studies, the team will obtain data to answer key questions for the planning of future studies and estimate parameters needed to inform the power analysis for a longitudinal study. The COVID-19 pandemic greatly affected this project. The Wien Center, which is the site of operations of the 1Florida ADRC, operated at limited capacity due to the COVID-19 pandemic periodically during the reporting period. There were changes in the research coordinator personnel at both the Mount St. Mary Center and University of Florida locations. There was a COVID-19 pandemic hiring delay of a lab technician to process the hair samples in Dr. Goldberger's lab. However, the team has been able to collect hair samples from 86 patients enrolled in the 1Florida ADRC. Cortisol measures of the hair samples, the appropriate data elements from NACC (National Alzheimer's Coordinating Center), and complete the statistical analysis.

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 #:** 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: It was attempted to create an Alzheimer's disease and related dementia (ADRD) prediction model using bioinformatic data gleaned from electronic medical records (EMR) and the OneFlorida Research Consortium (OneFlorida). We hoped to be able to predict ADRD 3-or 5-years in the future with sufficient precision that it would be clinically actionable. That is, we hoped to be able to implement the models into commercial EMR so that providers would be notified if a patient is at high risk of developing ADRD, even before symptoms start, so that interventions could be immediately implemented to slow or halt the neurodegenerative process.

However, after completing Aims 1 and Aims 2 of this project (creating a model using University of Florida (UF) Health interdisciplinary rounds (IDR), replicating UF model with OneFlorida data), the research team was unable to develop a model with sufficient accuracy and precision to be clinically actionable. That is, the research team was unable to produce a model with sufficient accuracy that a clinician would have a reasonable degree of certainty that a patient might develop ADRD without immediate intervention. Therefore, it was decided that the risk of implementing the ADRD algorithm into commercial EMR far outweighed the potential benefits.

Important key changes that occurred during the progress of the study was a change in the principal investigator. The initial principal investigator, Demetrius Maraganore, MD, was changed to Glenn Smith, PhD after creating the ADRD algorithms and exhausting all sound methodological options at improving classification accuracy, Dr. Bian, the lead data analytic specialist, reduced his efforts on this project from 5% to 1%, remained on the project as a consultant. We do not believe that either change in personnel/efforts adversely affected the outcome of this project. Our research team intends to repurpose the existent ADRD prediction model as a tool for recruiting healthy older adults unlikely to develop ADRD in the next five years. While the prediction model was poor at predicting patients who would go on to develop ADRD in the future (Sn = .56, PPV = .20), the model may be useful in recruiting patients who are unlikely to develop ADRD (NPV = .87). As such, current efforts are underway to use the model to recruit healthy subjects to serve as a healthy controls for a subsequent study that aims to collect normative data and validate neuropsychological assessments administered via telehealth (i.e., teleneuropsychology, [teleNP]). Using the OneFlorida IDR, the team can selectively recruit based on age, gender, race, ethnicity, rural/urban dwelling, and SES (by using zip code as proxy). Thus, the team are attempting to create one of the largest, most ethnically diverse normative dataset, to date. By creating a robust normative dataset, it is hoped to equip clinicians with a valid tool that can reach a broader patient population, helping to reduce healthcare disparities.

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 #:** 9AZ15 Association of PET Amyloid Status with Cognitive and Functional Outcomes of Behavioural Interventions in Mild Cognitive Impairment

Principal Investigator: Glen Smith, PhD

Organization: Univeristy of Florida

Abstract: Despite accumulating evidence that cognitive training (CT) and physical exercise (PE) can maintain specific cognitive and functional abilities, results are inconsistent as to whether CT and PE are effective interventions for delaying or slowing decline in people with MCI (pwMCI). Prior studies have inadequately accounted for the influence of the underlying pathology. Specifically, MCI behavioral trials have not fully investigated whether elevated beta-amyloid (A) levels, a hallmark biomarker of Alzheimer's Disease (AD), alters the efficacy of Computerized Tomography (CT) and PE on functional outcomes. Roughly 40% of pwMCI do not display pathological A levels on amyloid Positron Emission Tomography (PET) scanning. MCI can emerge from non-AD etiologies, including cerebrovascular disease and mood disturbances. The present study aims to characterize how the efficacy of CT and PE interventions in pwMCI associates with A status. Since amyloid scanning is very expensive, the research team will examine this association in a cost effective manner by utilizing participants from the Ed and Ethel Moore funded Physical Exercise And Cognitive Engagement Outcomes for Mild Neurocognitive Disorder (PEACEOFMND) trial. In that trial, almost 60 pwMCI were randomized to PE, computerized CT, or wellness education (active control) and followed for six months. We will re-engage and supplement those participants to obtain daily function outcomes at 18-months post intervention. The 60 pwMCI will be partitioned into tertiles based on Every Day Cognition (ECog) scale outcomes. The team will reduce PET costs by a third by scanning only those in the highest and lowest tertiles of ECog outcomes. This will nevertheless maintain the statistical power to detect medium to large effect. It is hypothesized that A+ pwMCI will be far more likely be in the lowest tertile of ECog outcomes. Additionally, exploratory analyses will explore if A status adds predictive power beyond baseline hippocampal volume in terms of functional outcomes. As a result of this project we conducted the first ever amyloid PET research scans at UF starting in December of 2019. Although the pandemic severely disrupted our data collection in 9AZ15, ultimately undermining the power to pursue the aims of the project, these scanning efforts were crucial in expediting the collection of amyloid PET as part of the new 1FL Alzheimer's Disease Research Center procedures. The 1FL ADRC was funded in June of 2020 with first time recruitment of 1FL ADRC core participants at UF.

Follow-on Funding: NIH/NIA; T32; Marsiske, Woods; $1,500,000.

Collaborations: The awarding of the grant contributed to the Florida Department and Health and lead to collaboration on the submisssion of a BOLD grant application to the the Centers for Disease Control.

Journals: Parahippocampal and temporal neocortical thickness as predictors of word-stem completion priming in individuals with amnestic Mild Cognitive Impairment. De Wit, L., Tanner, J.,Lambertus, T.,Chandler, M., Smith, G. Neurobiology of Learning and Memory. 2021.

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Comparative effects of physical exercise and other behavioral interventions on functional status outcomes in mild cognitive impairment. Shandera-Ochsner, A L., Chandler, M.J., Locke, D.E.C., Ball, C.T., Crook, J.E., Phatak, V.S., Smith, G.E. Journal of the International Neuropsychological Society. 2021.

Modular Machine Learning for Alzheimer's Disease Classification from Retinal Vasculature. Tian, JQ, Smith, G, Guo, H, Liu, B, Pan, Z, Wang, Z., Xiong, S., Fang, R. Scientific Reports. 2020.

Repetition Priming in individuals with amnestic Mild Cognitive Impairment and Alzheimer's dementia: a Systematic Review and Meta-Analysis. De Wit, L., Piai, V., Thangwaritorn, P., Johnson, O'Shea, D., Amofa, P., Marsiske, M., Kessels, R., Schaefer, N., Smith, G.E. Neuroscience and Biobehavioral Reviews. 2020.

Psychometric Properties of a Memory-Related Self- Efficacy Scale in Mild Cognitive Impairment. International Journal of Psychogeriatrics. International Journal of Psychogeriatrics. 2020.

Comparative Effectiveness of Behavioral Interventions to Prevent or Delay Dementia: One-Year Partner Outcomes. Amofa Sr, P., Locke, D.E.C., Chandler, M., De Wit, L Ball, C. T., Phatak, V., Crook, J., Smith, G.E. 2020.

Patents: None at the time of reporting.

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

Principal Investigator: Gordon Mitchell, PhD

Organization: University of Florida

Abstract: At the time of this report, we remain in the process of completing key goals of this project, although we have made significant progress in a number of areas. In specific, afer recruiting a postdoctoral associate to move this research forward, the research team was able to: complete analyses of tau-phosphorylation state in brains previously collected from normal rats exposed to three different intermittent hypoxia protocols (ranging from therapeutic and pathogenic). Although these rats were from another project, the research team was able to take advantage of their availability to advance the scientific goals articulated in the present grant. Secondly, expose sets of young and old transgenic mice over-expressing mutant tau (and non-transgenic mice) to chronic intermittent hypoxia and harvest their brains for analysis. The biochemical analyses of these tissues are still ongoing. Progress in this area was greatly hindered by the pandemic, which required a research slowdown and culling of mouse colonies during the spring of 2020. It took some time to breed new mice that would be used in the studies funded by this grant. Alternate sources of funding to complete these biochemical analyses are being sought. Lastly, before mice were exposed to intermittent hypoxia and sacrificed, they were placed in a barometric plethysmograph to record breathing patterns: remarkable patterns were observed some, reminiscent of the sleep apnea common to most individuals with Alzheimer's Disease (AD). Although analyses are still underway, these bonus findings will set

the stage for a new research direction into an unexplored topic in AD research: the pathogenesis of sleep apnea in people with AD. Future plans are to finish experiments needed to complete Aim 1, which explores the effects of chronic intermittent hypoxia characteristic of sleep apnea on development and progression of tau pathology. Despite discontinued support, future opportunities may include experiments to explore the effects of acute intermittent hypoxia on tau pathology from Aim 2 and/or the pathogenesis of sleep apnea 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.

14. **Grant #:** 9AZ17 Mechanisms of Abnormal Neuronal Tau Cccumulation, Interactions with Amyloid-Beta and Pathological Sequelae

Principal Investigator: Benoit Giasson, PhD

Organization: University of Florida

Abstract: Brain neuronal inclusions comprised of tau and extracellular deposits of Abeta peptides are diagnostic criteria of Alzheimer's Disease (AD). In AD, tau aggregates as dystrophic neurites in neuronal processes within Abeta senile plaques and as somatodendritic inclusions in the form of neurofibrillary tangles (NFTs) and neuropil threads. Importantly, tau mutants are sufficient to cause ADrelated dementia disorder. Tau is a microtubule (MT) associated protein normally primarily located in neuronal axons. In AD and patients with tau mutations there is an abnormal redistribution of tau within somatodendritic cellular compartments, presumably resulting in its aggregation and neurotoxicity. However, the mechanism(s) involved in this abnormal localization and the interactions synergizing tau and Abeta pathologies in AD remain largely poorly understood. Many tau mutations have been reported to significantly lower tau's interact with MT, the major mechanism involved in tau axonal transport. However, mutations such as Q336R and Q336H increase MT binding *in vitro*, suggesting that different types of imbalances in the MT binding properties of tau is sufficient to cause neurodegeneration. Nevertheless, these possible paradigm shifting findings remain limited to *in vitro* data. We propose the following Specific Aims to investigate the properties of specific pathogenic tau mutants (P301S, P364S, Q336R and Q336H) compared to wild type tau on tau-MT interactions, tau aggregation propensities, neuronal localization and distribution, and the pathological sequela associated with these changes as well as the influence of Abeta deposition on these processes *in vivo*. In the eighth quarter of this grant, research staff continued to work on some of the studies described in the Specific Aims. The studies on the cellular and biochemical assessment of Q336H and Q336R tau mutations in terms of prion-like seeded aggregation and changes in microtubules interactions properties in 293T cells very completed such that they were now accepted for publication.

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

Collaborations: None at the time of reporting.

Journals: Xia, Y., Nasif, L., Giasson, B.I. (2021) Pathogenic MAPT mutations Q336H and Q336R have isoform- dependent differences in aggregation propensity and MT dysfunction. J. Neurochem. (on-line) https://pubmed.ncbi.nlm.nih.gov/33772783/

Patents: None at the time of reporting.

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

Principal Investigator: Neal Jeffrey Weisbrod, MD

Organization: University of Florida

Abstract: This project aimed to further investigate the importance of establishing advance care planning during early dementia diagnosis. Along with establishing early care planning, this study also wanted to investigate the patient and clinician relationship after the diagnosis has been made. With this study design, the project was primarily recruiting from the Fixel Institute of Neurological Diseases. The patients were pre-screening for a mild cognitive impairment (MCI), dementia, or Alzheimer's Disease (AD) referral. Participants then qualified for the study if the principal investigators (PIs) classified them under an MCI or mild dementia diagnosis. Once enrolled there was an initial visit phone call where the HADS and Behavioral Health Services (BHS) were administered and a second clinic visit to follow up from their initial evaluation. At this second clinic visit, the intervention group would discuss the use of an advance directive and attempt to establish an advance care plan during the visit. The control group would conduct their visits as part of their normal care routine. After the second visit, another research phone call would be conducted and the HADS and BHS would be administered for a second time to both the participant and the caregiver (if applicable). Medical record reviews would be conducted at three follow-up time points post clinic visit. As a result, the study enrolled 25 participants into the intervention group (15 patients and nine caregivers) and 13 participants into the control group (seven patients and six caregivers). Of the intervention group, four patients had record of completing an advance care directive and one participant/caregiver dyad withdrew. Of the control group, one patient had record of completing an advance care directive and one participant/caregiver dyad withdrew. This study did experience many challenges over the last few years, mainly the COVID-19 pandemic and staffing changes. The COVID-19 pandemic closed the clinics for roughly four months and cause a pause in research related activities for roughly six to nine months. While the study staff was able to conduct phone call visits, recruitment and enrollment was decreased due to the pandemic limitations. Currently, there is no future funding to further investigate this work in the clinical setting, however, the PIs will continue to advise and encourage patients to become familiar with advance care planning. The research PIs discovered positive qualitative feedback from participants in the intervention group and participants felt as if the challenging conversations assisted in their understanding and management of the disease diagnosis.

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 #:** 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: The purpose of this funded Ed and Ethel Moore Alzheimer's Disease (AD) research investigation was to examine if individuals with early forms of neurodegenerative disease markers (as seen on Magnetic Resonance Imaging (MRI) and cognitively) would respond differently (cognitively and via neuroimaging metrics) to general and spinal anesthesia during their elective total knee arthroplasty surgery. The proposal was based on a successful NIH R01 investigation conducted by the primary investigator and the investigative team (Mareci, Tanner, Ding) reporting how specific preoperative markers of brain and cognitive vulnerability predicted acute free water and functional neuroimaging changes for older adults electing total knee replacement with general anesthesia. Resulting R01 publications (e.g., Huang, Tanner, et al., 2018; Hardcastle et al., 2019; Tanner et al., 2019) showed individuals with reduced cognition had atypical changes in functional network and free water after surgery. All R01 surgery participants had received general anesthesia (n=64 surgery). It was consequently questioned if this response was partially attributable to a negative interaction with the anesthesia. Would spinal or regional anesthesia approach be less compromising to the brain? For this primary reason, the current project was designed as a randomized study for spinal/general administration recruiting individuals age 65 or older who were electing total knee replacement.

The project faced many unexpected challenges that impacted research productivity over the course of 2.5 years. First, staff experienced an unexpected patient dislike for anesthesia randomization. Although there is no research demonstrating that general is worse or better than spinal/regional anesthesia approaches, a large portion of patients staff approached about the study refused to participate due to the element of randomization. Second, it was experienced a change in hospital discharge options presented to patients. Although the study was prospectively created with one surgeon (which then expanded to three surgeons), the hospital discharge for older adults electing orthopedic surgery changed to discharge the same day of surgery. This means, individuals electing surgery were often informed they could leave the hospital the same day of surgery. Although the investigative surgeons agreed to participants for more than one night, the patients often wanted to go home the same day. This compromised the agreement to be involved in an acute postoperative MRI (which was one of our main objectives in order to match to the original parent study). Third, a shutdown due to COVID-19. Elective surgeries were shutdown from March 2020-May 2020, and during Delta variant spikes from July 2021-September 2021. There was also a slow return to face-to-face research assessments within UF due to the pandemic. The research team consequently faced a significant reduction in recruitment potential despite Investigational Review Board changes increasing the surgeons from one to three, removing randomization as a requirement, and removing the acute MRI necessity. These changes are described in the previous progress reports and request for no-cost extension.

Despite the smaller sample size, the pilot data shows how spinal versus general may result in differential acute free water and functional MRI status. There was not enough of a sample size,

however, to demonstrate how baseline cognitive function or brain integrity interact with anesthesia type to produce different outcomes. This is highly unfortunate as the study is needed to address how preoperative brain integrity interacted with anesthesia type. Data are being used in a paper publication pending final submission December 2021, have been used in a recent R01 submission addressing free water mechanisms in neurodegenerative disorders, and will be incorporated in a NIH program grant as part of the perioperative cognitive anesthesia network program for AD and related dementias. Researchers learned that individuals do not wish to partake in randomization options (spinal/general). For this reason, the PI and team have decided to forgo plans for a larger randomization study. Additionally, given the hospitals changes in orthopedic surgery same day discharge (even for "major" surgeries such as total knee or hip replacement), the investigators will no longer look at acute MRI changes. Future studies will address three week and three month changes.

Follow-on Funding:

PROPOSAL/GRANT TITLE: Perioperative Cognitive Anesthesia Network Program for ADRD. NIH. Catherine Price. $810,00.

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

17. **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: After obtaining the Institutional Review Board (IRB) approval, research staff earnestly started pre-screening patients seen at the Cognitive Disorder Clinics (Department of Neurology, University of Miami) and identified patients suitable to participate in this study. The procedures of this study require physical visits of participants to the UM Medical campus, and these include a brain MRI scan, a blood draw, a stool sample collection and a battery of neurocognitive tests.

The research team has prescreened over 200 subjects that includes patients and their spouses. We enrolled eight subjects into the study until the second week of March 2020 and have completed the study procedures of them. Due to the COVID-19 pandemic, the University of Miami (UM) did not permit our research team to conduct studies with participants from the third week of March through 9/23/2020. In an effort to enroll and complete at least part of the study procedures during the pandemic period, staff made appropriate changes to the study protocol, primarily to obtain neurocognitive and nutritional intake data via a Telehealth Platform, and obtained IRB approval for this modification. Since patients are utilizing the UM Telehealth Platform these days for their visits with doctors at the UM Clinics, our efforts have not helped us to recruit many participants. The research team resumed the regular study activities since 9/24/2020. However, since the COVID-19 pandemic is still prevailing, the University of Miami (UM) Office of Research Administration has limited our access to potential patients at the UM Clinics. So, unfortunately, the prevailing COVID-19 pandemic situation made subject

recruitment and sample collection activities still difficult and we were unable to enroll additional subjects into the 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.

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

Principal Investigator: Rosie E. Curiel Cid, PsyD

Organization: University of Miami

Abstract: Dr. Katherine Gorman is a Doctor in Clinical Psychology that completed her first year of fellowship training at the Center for Cognitive Neuroscience and Aging (CNSA) at the University of Miami Miller School of Medicine. The fellowship commenced on July 22, 2019 and ended on July 21, 2020.

Dr. Gorman received training across every one of our scientific protocols, which included two longitudinal R01 studies funded by the National Institutes of Health and several state grants, all of which are related to early detection of Alzheimer's Disease Related Dementia (ADRD). In addition, he provided clinical neuropsychological evaluations in our state-funded Memory Disorders Clinic. Dr. Gorman also engaged in the supervision and mentoring to pre-doctoral students from various local training programs. The post-doctoral fellow was a scientific contributor on a poster presentation presented at the National Academy of Neuropsychology Meeting and also contributed to a peer-reviewed publication as well as a peer-reviewed publication. Due to the excellent performance and strong interest in continuing to develop her clinical research skills, she was awarded a second year of postdoctoral training at the Center. This is required for specialty practice in Neuropsychology.

Dr. Gorman's role in the program of research grew to be versatile. Dr. Gorman worked with the study team to ensure the proper implementation of the scientific protocols, conducted standardized administration, scoring and interpretation of a broad range of neuropsychological tests (traditional and novel). This researcher consented participants for clinical and biomarker procedures and conducted assessments to be an active participant in our consensus diagnosis meetings. Dr. Gorman also interfaced with multidisciplinary collaborators from other departments including radiology and nuclear medicine to facilitate our neuroimaging studies including Magnetic Resonance Imaging (MRI), amyloid and tau Positron Emission Tomography (PET) imaging, and blood biomarkers.

Dr. Gorman is an excellent and valued team member and most recently provided substantial input to move our research visits to a telehealth platform given the limitations imposed by the COVID-19 pandemic. This researcher was a true leader in this regard and worked closely with a team of collaborators in the Center created a step-by-step manual to ensure fidelity to protocols, procedures, and standardized administration in a valid manner over this virtual platform. Dr. Gorman has now initiated a second year of training in neuropsychology and cognitive neuroscience at our Center, which is required for specialty practice in neuropsychology. Dr.

Gorman is doing so under the supervision of Dr. Rosie Curiel and co-Mentor, Dr. David Loewenstein. This is required for specialty practice in Neuropsychology. Dr. Gorman has taken a greater leadership role over time andd expressed her interest in becoming more involved in scientific input and analyses and is working on contributing to additional manuscripts and has developed trainings for the study team.

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

Collaborations: None at the time of reporting.

Journals: Diagnostic Utility of Visual and Verbal Memory Tests Among Older Adults at Risk for Alzheimer's Disease. Miriam, J., Rodriguez PhD, Katherine Gorman, PsyD, Rosie Curiel PsyD, Ranjan Duara M.D. & David A. Loewenstein PhD. Aging, Neuropsychology and Cognition. 2020.

Patents: None at the time of reporting.

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

Principal Investigator: Philip Harvey, PhD

Organization: University of Miami

Abstract: The project assessed and quantified the effect of poor sleep quality and cerebral vascular disease on cognitively critical brain regions which are involved in the pathophysiology of dementia of the Alzheimer disease (AD) type. It has been well documented that poor sleep quality is strongly associated with AD. However, it has not been widely investigated how poor sleep impacts elderly subjects who are not demented, i.e., cognitively normal. The researchers studied the effect of poor sleep in normal elderly community-dweller subjects ages 60 to 80 years and found that poor sleep has a significant negative impact on brain health. Compared with good sleepers, poor sleepers have significantly smaller cognitively critical brain regions (e.g., hippocampus, superior parietal lobules, and the amygdala, on the order of 7% smaller volumes. This important finding was published in 2019 in the main sleep journal. This finding implies that sleep intervention should be considered well prior to onset of cognitive decline in order to slow down progression to dementia. Secondly, we further investigated which sub-regions of the hippocampus (i.e., hippocampal subfields) were smaller in the poor sleepers and found two regions that are significantly impacted in the poor sleepers. This finding has been recently accepted for publication in the journal Sleep Research.

The project assessed and quantified the effect of poor sleep quality and cerebral vascular disease on cognitively critical brain regions which are involved in the pathophysiology of dementia of the Alzheimer disease (AD) type. It has been well documented that poor sleep quality is strongly associated with AD. However, it has not been widely investigated how poor sleep impacts elderly subjects who are not demented, i.e., cognitively normal. The research team studied the effect of poor sleep in normal elderly community-dweller subjects ages 60 to 80 years and found that poor sleep has a significant negative impact on brain health. Compared with good sleepers, poor sleepers have significantly smaller cognitively critical brain regions (e.g., hippocampus, superior parietal lobules, and the amygdala, on the order of 7% smaller volumes. This important finding was published in 2019 in the main sleep journal. This finding implies that sleep intervention should be considered well prior to onset of cognitive decline in

order to slow down progression to dementia. Secondly, it was further investigated which sub-regions of the hippocampus (i.e., hippocampal subfields) were smaller in the poor sleepers and found two regions that are significantly impacted in the poor sleepers. The plan is to investigate the mechanism by which poor sleep impacts brain health.

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

Collaborations: None at the time of reporting.

Journals: Alperin N, Wiltshire J, Lee, AR Ramos SH, Hernandez-Cardenache R, et al. Effect of sleep quality on amnestic mild cognitive impairment vulnerable brain regions in cognitively normal elderly individuals. Sleep 42 (3), zsy254, March 2019, PMID: 30541112.

Liu C, Lee SH, Loewenstein D, Hernandez-Cardenache R, Alperin N. Effect of Sleep Quality on Hippocampal Subfields in Cognitively Normal Elderly Individuals. 2021 Sleep Research.

Patents: None at the time of reporting.

20. **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: The proposed pilot study examines the relationship of greenness to Alzheimer's Disease (AD) incidence, comparing International Classification of Diseases (ICD) code diagnoses in Medicare beneficiaries from 2010 and 2016. National Aeronautics and Space Administration (NASA) satellite imagery will be used to calculate block-level Normalized Difference Vegetation Index (NDVI) to be used as greenness scores for 2010 and 2016. The research team will code the available universe of all ~9,000 low-income Census blocks in Miami-Dade County into three block types based on their greenness scores: 1) Low-Low: lowgreen blocks in 2010 with no tree plantings; 2) High-High: high-green blocks in both 2010 and 2016; and 3) Low-High Blocks: low green blocks in 2010 with tree-plantings resulting in high greenness in 2016. Utilizing propensity scores as a statistical matching technique, the team will randomly select 1,000 blocks in each of the three block types. Multi-level modeling will be used to test the impact of greenness (Low-Low blocks vs. High-High blocks) and tree-planting (Low-Low blocks vs. Low-Highblocks) on AD incidence.Future plans include conducting further programmatic, prospective longitudinal research studies as is needed to better establish causality, as well as examining further mechanisms through which greenness may lead to lower risk of developing Alzheimer's disease and related dementias (ADRD) over time.

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

Collaborations: None at the time of reporting.

Journals: Relationship of Neighborhood Greenness to Alzheimer's Disease and Non-Alzheimer's Dementia Among 249,405 U.S. Medicare Beneficiaries. Aitken, W.W., Lombard, J., Wang, K., Toro, M., Byrne, M., Nardi, M.I., Kardys, J., Parrish, A., Dong, C., Szapocznik, J., Rundek, T., Brown, S.C., Journal of Alzheimer's Disease. 2021.

Block-level Greenness Associated with Lower Odds of Depression Among Older Adults in Miami-Dade County. Brown, S.C., Perrino, T., Lombard, J., Szapocznik, J., British Journal of Psychiatry. 2020.

Patents: None at the time of reporting.

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

Principal Investigator: David Lowenstein, PhD

Organization: University of Miami

Abstract: The vast majority of cases diagnosed with Alzheimer's Disease (AD) are considered late onset (LOAD). Previously, in a small cohort in Buenos Aires, our 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. 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 Hispanic middle-aged children which 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. The research team 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 Magnetic Resonance Imaging (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 investigators are in the process of conducting preliminary data analyses. Specifically, we are examining whether O-LOAD have early LASSI-L cognitive deficits on subcales susceptible to proactive semantic interference (PSI) and failure to recover from proactive semantic interference (frPSI). We are also in the process of examining whether these deficits are related to both functional and structural MRI findings as well as genetic risk.

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

Collaborations: Three postdoctoral research fellows are currently collaborating in the research activities.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

22. **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, MD, PhD

Organization: University of Miami

Abstract: This study has uniquely accomplished new data and for the first time created Magnetic Resonance Imaging (MRI) Quality Control (QC) and the MRI analytical pipelines that did not exist before in One Florida Alzheimer's Disease Research Center (1FL ADRC) nor it was broadly available nationwide. This was an important step and unique deliverable of this project. The QC and postprocessed MRI scans are now available for sharing with 1FL ADRC investigators to evaluate the effect of MRI biomarkers on multiple cognitive outcomes and clinical conditions. We have also created several software program codes for semi-automated and automated image processing. This unique study has, for the first time, determined the burden and the impact of the modifiable vascular risk factors, comorbidities on vascular brain imaging phenotypes and cognition and the signatures of AD pathology in the 1FL ADRC population. This study is of high impact for the health of the Florida population, as it helps closing the gap in our understanding of the mechanisms by which vascular phenotypes contribute to AD pathology and inform strategies to reduce AD risk specifically tailored to high vascular and AD risk individuals in the diverse Florida population.

In addition, this research has created a valuable multi-disciplinary team that includes neurologist, radiologists, physicists, psychologists, data base managers, and statisticians. The team also includes MD and PhD students and postdoctoral trainees including residents and fellows, who performed some of the analyses and obtained hands-on research training in fundamentals of neuroimaging, cognitive neurology, aging and research methods. The team also has learned the science of team science from successfully working within a team, from storming, norming and performing, negotiation, leadership, and working collaboratively for successful accomplishments of our objectives.

One of the most notable achievements of the team was a successful competitive renewal of 1FL ADRC at the NIA in 2020. The research team has obtained a large multi-center grant to fund infrastructure for 1 FL ADRC, for which our team members serve as Pis for the University of Miami and co-leads of 1FL ADRC Clinical Core and Research Education Core. In addition, we have secured a continuation of our VIP study through FL DOH funding and extended the VIP study to include carotid subclinical atherosclerosis using a high resolution ultrasound technology. The team has already extended research of this study by continued enrollment in 1FL ADRC, secured funding for 1FL ADRC, and extended VIP study to investigate novel subclinical markers of vascular disease (ultrasonographic measures of carotid intima media thickness, Intima-media thickness (IMT) and plaque presence, size and morphology). This line of research bringing vascular phenotypes to neurodegenerative pathology is very innovative and we have secured funding to perform a high-resolution carotid ultrasound in a sample of 1FL ADRC participants through new FLDOH award. This grant will help generate pilot data in order to proceed with a large application for the NIH funding. As soon as we publish more data from the current research and obtain pilot data using new FL DOH funding we will collaboratively apply for an NIA research grant to study imaging biomarkers of subclinical atherosclerosis in AD and other neurodegenerative disorders.

Follow-on Funding: 1Florida Alzheimer's Disease Research Center (1FL ADRC). Golde/Loewenstein/Duara. $15,304,131

Carotid Ultrasound Imagin Markers of AGINg and Endothelial Function in Risk of Alzheimer's Disease: the Florida IMAGINE Study of AD Risk. FL DOH-21A20. $247,620.

Collaborations: The investigators from the University of Miami (PI and other investigators) developed new and close relationships and collaborations with the investigators from the Mount Sinai's Wien Center for Alzheimer's Disease and Memory Disorders, Florida University

Journals: Utility of Plasma Neurofilament Light in the 1Florida Alzheimer's Disease Research Center (ADRC) Barker W, Quinonez C, Greig MT, Behar R, Chirinos C, Rodriguez RA, Rosselli M, Rodriguez MJ, Cid RC, Rundek T, McFarland K, Hanson K, Smith G, DeKosky S, Vaillancourt D, Adjouadi M, Marsiske M, Ertekin-Taner N, Golde T, Loewenstein DA, Duara R. JAD 2021;79(1):59-70. doi: 10.3233/JAD- 200901.

Patents: None at the time of reporting.

23. **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: There were a total of 23 administrators and nurses in the sample. A total of 126 residents in 10 Assisted Living (AL) recruited. All baseline and three month data has been collected in nine sites and baseline in one site that was recruited in February, 2021. Six month data was collected in eight sites (one AL site dropped out after the three-month data collection nperiod due to COVID-19). Sites 11 and 12 were recruited in late February but did not begin after the end of the project end date and a no cost extension was not granted. These two sites will be included but under a different approved Institutional Review Board for the project since the funding ended for this project. One control site dropped out after the three-month follow-up due to COVID-19 restrictions and nurse attrition. All data that has been collected at baseline, three and six-months for the residents has been entered except for site 10 that has just baseline data completed so far. All staff (N=23) who have participated in the training and control sites data has been entered. The last treatment site was unable to receive gift cards before the end date of the project so we used University of South Florida indirect funds.

In August 2020, the research team presented findings about the PCEAL intervention and the staff outcome of palliative care knowledge at the Florida Conference on Aging online in a workshop titled "Formal and Informal Caregiver Research Across the Continuum." A variation of this presentation was also presented as part of a symposium in November 2020 for the Gerontological Society of America virtual conference. Below in Table 1 is a description of the nurse and administrative sample. The recruitment has been opened up to administrators in AL because we are learning that some ALs do not have a nurse that is an employee but use home health care nursing staff. We will use the indirect funds from this project to pay a research assistant to continue collecting the remaining data from the three ALs and to give participants gift cards in those three ALs. The remaining data collection should be completed by August, 2021. We are in the process of writing a protocol paper for a nursing journal hoping to submit in early June. We are planning for either a June or October, 2021 submission for an R01 large federal grant to the National Institute of Aging to sample ALs that have existing relationships with four area hospices owned by either Empath Health or Chapters Health (Suncoast, LifePath Hernando Pasco Hospice, Tidewell) and Community Hospice in Jacksonville to recruit 30 ALs and a sample of 300 residents and their family members, and 60 AL staff (nurses, dementia

care coordinators, social workers and administrators). The number of ALs, residents, family and staff is feasible and realistic for a three year project. These changes make the project substantially different and the aims would be different with the primary aim as family satisfaction with care and increased documentation of Advanced Care Planning (ACP) discussions. With our preliminary data for the ACP discussions outcome, there are significant increases in the treatment group compared to the control group. The team has not looked yet at the data for hospice referrals and admissions, the secondary study outcome, and the team has have not completed our analysis for the second aim, mediation analysis for primary care knowledge increase and if that mediates our primary patient-centered outcomes. The National Institute on Aging has additional funding for projects that are studying dementia populations. Some changes for a larger randomized control trial would include family outcome data on the perceptions of end of life care. The team, also would design the study with what we have learned, with the hospices offering the PCEAL program to AL sites instead of in the current project, once an AL is identified, we coordinate with the hospice to facilitate the training.

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

Collaborations: We continue to collaborate with Hospice organizations including LifePath Hospice of Chapter's Health and Suncoast Hospice of Empath Health. For the larger project, as described in this report, we will work with the hospices to enroll new ALs in the PCEAL.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

24. **Grant #:** 9AZ27 Structure and Toxicity of Amyloid Beta Hetero-Oligomers

Principal Investigator: Kyaien O. Conner, PhD, LSW, PMH

Organization: University of Central Florida

Abstract: Culturally relevant non-pharmacological approaches to optimize the functioning of African Americans living with Alzheimer's disease (AD), reduce caregiver stress and provide personcentered care practices are urgently needed. African Americans have a disproportionately high rate of AD, experience a high-rate of AD-related health disparities, and are underrepresented in AD research. Music interventions are low-cost interventions with benefits reported in previous studies including improvements on measures of anxiety and depression, agitation, mood and autobiographical memory recall. African drumming may be particularly beneficial for African Americans living with AD. This culturally relevant and personalized approach to a music intervention has the potential to enhance the social environment for African Americans with AD and caregivers, reduce caregiver burden, improve mood and quality of life while simultaneously enhancing self-esteem and self-efficacy. The current proposal supports the implementation and assessment of the feasibility and acceptability of an innovative African Drumming for Dementia intervention. It is proposed an open trial whereby we will pilot test and determine the feasibility of the African Drumming for Dementia intervention for community dwelling African Americans with early stage AD (N= 30) and caregivers (N=30). The research team has made many scientific accomplishments over the course of this project. In previous reporting periods, it was developed a strong collaboration with our community partner, got our institutional review board approved, and built our research

database. By reporting period three the research team completed recruitment for our first Drumming for Dementia intervention groups (one caregiver and one person living with dementia/ participant group). The first intervention groups began on October 2nd at 3:30pm and our caregiver group began at 4:30pm. The eight-week intervention ran successfully and ended on November 20th. The research team had a small celebration with the participants and caregivers who completed the intervention on December 4th, 2019. At this celebration, both groups were able to showcase to loved ones and the rest of the center what had been learned over the eight-week group. Participants all also received certificates highlighting their completion of intervention.

Data was entered for all 18 participants for our first two intervention groups. The team collected baseline data from all participants, and completed follow-up assessments for 10 participants. We further conducted qualitative interviews with five participant-caregivers. Satisfaction surveys and interviews suggest this intervention is acceptable to participants and additional interviews with staff suggest this intervention is feasible and that sites have enjoyed having this extra component to their therapeutic programs. The team received three letters from caregivers, independent of this research, outlining how loved ones benefited from this intervention and how they would like to continue to engage in this intervention were it to be made available on a more consistent basis. By reporting period four we had analyzed preliminary data from those groups frothe baseline to post intervention assessments. All outcomes were in the expected direction, and we found the intervention to be feasible and acceptable to the population. The team began recruiting at that time for our second two intervention groups.

The team began two virtual Drumming for Dementia intervention groups with four caregivers and four people living with dementia on June 30th 2021 which ended on August 25th 2021. Two participants from the aforementioned group dropped out due to participant illness. The team also began a third virtual intervention group on July 2nd 20201 which ended on August 20th 2021. This third intervention group only involved only 10 older adults at risk of AD, without a caregiver group. This group came from older adult participants who wanted to join the Drumming for Dementia program, but did not have an active caregiver who could participate in the program. Ultimately, a total of 36 participants were recruited and participated in our programs. And have collected data on all participants. Final follow up assessments were conducted the weeks of October 25, 2021 until November 4, 2021. This later date for the final assessments was needed due to following the protocol which had assessments due two months post intervention. The team also had a few storms and hurricanes in Florida that created technology challenges, which impacted our start dates. Despite our challenges, the team has made many scientific accomplishments on this project since initial funding and has successfully run five intervention groups of the Drumming for Dementia program. We ran two groups in-person, and three groups virtually. There have been no personnel changes during the course of this project. The major challenge has been the COVID-19 pandemic. Due to the pandemic and the concern for vulnerable older adults, all of our adult day care sites have been shut down and still have not re-opened. It required stopping our project for a significant period of time, reframing our methodology and intervention delivery, and additional challenges not anticipated during our initial proposal submission. However, this shift also provided us a unique opportunity. An opportunity to evaluate a virtual version of the Drumming for Dementia intervention, the ability to connect with isolated and lonely seniors, and burdened caregivers, looking for an opportunity to reconnect with their peers and alleviate stress as well as other psychosocial concerns and symptoms. The team developed sufficient pilot data for a submission to test this

"virtual" intervention on a larger scale. The research has led to some exciting preliminary findings. That the Drumming for Dementia Intervention is feasible, and acceptable to participants, and can impact important psychosocial outcomes for older adults with early-stage AD, at risk for AD and their caregivers. The research also learned that conducting this program virtually may be beneficial for these participants, and can provide access to social engagement activities for isolated older adults who are unable to go to a senior or adult day care center. If these findings hold after our final follow up assessments are complete, and final data analysis is conducted, it will be the goal to move this program forward by submitting a proposal for a larger trial to test both a face-to face and virtual version of the Drumming for Dementia program. The team also learned, that this program may be beneficial not only for older African Americans, but as well for older Latin populations and non-Hispanic White populations. In future research, we would plan to have a racially diverse sample population, evenly stratified by race, to look at potential racial/ethnic differences in outcomes.

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

Principal Investigator: Hongdao Meng, PMH, PhD

Organization: University of South Florida

Abstract: Providing support to persons living with dementia (PLWD) and informal caregivers (ICGs) is critically important in maximizing aging-in-place and reducing the disease burden of dementia. To date, evidence-based PLWD/ICG interventions often require substantial time and travel commitment from the participants, which often limits participation. The objective of this study is to develop, manualize, and pilot test an innovative Visually-Assisted Mindful Music Listening (VAMML) intervention, which consists of four weekly guided appreciation sessions at an Adult Day Care Center, supplemented by daily assigned listening sessions. The key component of the intervention is the Tropical Sweets® DVD/mobile music collection developed by a master musician-educator in Florida. This commercially available music video utilizes artfully interwoven nature and space imagery to engage participants eyes in the process of listening to carefully chosen relaxing music with specifically written guides to facilitate mindful music appreciation. In this pilot project, we will develop a standard training manual for formal implementation of the VAMML intervention in the Adult Day Care centers, in the home and other community settings. We will partner with the Hillsborough County Department of Aging Services to recruit volunteer participants. The most significant scientific accomplishments made by the research project include: completion of the patient (persons living with dementia) intervention design; completion of the patient portion of the study and confirmed the feasibility and acceptability of the group music intervention for persons living with dementia in assisted living and adult day service center communities; demonstrated preliminary efficacy of the intervention on agitation among persons living with dementia. The team achieved the primary goal of

developing a novel group music intervention for memory care. The immediate next step would be to conduct a randomized efficacy trial in more memory care communities, followed by a large multi-center randomized effectiveness trial. The team is actively seeking funding to support these efforts.

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

Collaborations: This research enables a new collaboration with Dr. Pratool Bharti at Northern Illinois University.

Journals: None at the time of reporting.

Patents: USF intervention disclosure: Group-based multi-modal music intervention to enhance well being and reduce behavioral expressions for persons living with dementia in memory care communties, filed on February 16, 2021.

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

Principal Investigator: J. Matt Webster, PhD

Organization: University of South Florida

Abstract: Scientists have developed a strategy for developing a tripartite library using the Caspid Scaffolding Protein (CSP) scaffold displayed on T7 phage. The goal library diversity per pilot-sized batch was at least 1 x 107. Scientists created our first pilot CSP library with a diversity of ~2 x 106 and then made changes to our library design strategy to optimize for increased diversity. The latest strategy yielded a raw diversity of 6.7 x 107 with 86 % correct full-length clones. The team anticipates, based on this assessment, that the final tripartite library will have ~1 x 109 diversity. The team has also started optimizing biopanning conditions using the small pilot library and are seeing some anti-tau enrichment resulting in a series of clones with variable binding to tau.by enzyme linked immunoabsorbant assay (ELISA). Additionally, the rationally designed CSP-PHF6 construct was evaluated in a cellular tau accumulation and aggregation assay, wherein the team did see a decrease in mutant tau protein levels with co-expression of CSP-PHF6. The team will scale up the CSP-L library, as well as the CSP-F and CSP-K library, to create a tripartite library with ~1 x 109 unique clones. Once created this library will be amplified and stored; which can be used to screen for binders against any target. Researchers will also use this large library to screen against monomeric tau and tau oligomers evaluated by ELISA. The highest affinity anti-tau phage clones will be sequenced and used to create mammalian expression plasmids for evaluation in a cell model of tau aggregation. Future plans for this project will be to use this preliminary data apply for grants to continued development of anti-tau binders on this scaffold. These will include monomeric, oligomeric, fibrillar and phosphorylated forms of tau. Anti-tau CSP variants can be used on their own or as a part of a modular fusion protein to develop constructs that reduce tau accumulation or aggregation. Additional intracellular effectors of neurodegenerative progression could similarly be targeted to create functional intracellular binding proteins using the CSP scaffold. It is planned to submit grant applications to NSF and NIH which will include academic research grants and SBIR/STTR applications. The USF tech transfer office is in the process of creating a patent application. Researchers have created a new business entity (AffiRock Biologics) through which will be used to pursue investment for commercialization of this protein scaffold.

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

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: A provisional patent application was submitted in January 2021. We are working on a full patent application prior to the one year anniversary of the provisional application.

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

Principal Investigator: Crystal Bennett, PhD, RM

Organization: University of West Florida

Abstract: The proposed project will address a major problem in the management of neuropsychiatric symptoms in Alzheimer's disease and related dementia disorder (ADRD) persons in Northwest Florida through the development of a safe and low-cost non-pharmacologic approach. In addition, these symptoms are accompanied by altered physical function and caregiver burden that contribute to poorer health for both the ADRD person and the caregiver. Commonly, these neuropsychiatric symptoms are treated with expensive and harmful antipsychotic medications that are known to contribute to increased mortality for ADRD persons. Non-pharmacologic approaches are recommended as first-line treatment for neuropsychiatric symptoms and need to be implemented with the ADRD population to reduce the use of harmful medications. The population that will benefit the most from this project are ADRD residents of assisted living facilities (ALF) and their caregivers. In total 40% of ALF residents have ADRD and evidence suggests that current ALF activities provide inadequate stimulation and do not provide optimal benefits. The health impacts of this proposed project will have multiple positive effects that include reducing agitation; improving balance, gait, and lower extremity function; and reducing caregiver burden. The most significant accomplishments to date are implementation of project at one assisted living facility for a period of 24 weeks, meetings with consultant to review adapted dance choreography as well as changes needed to intervention, and recruitment of participants with modified protocol as a result of COVID-19 restrictions in assisted living facilities. Important changes that have unfavorably impacted the research is the COVID-19 interruption that led to the inability to begin recruitment and implement project at another assisted living facility.

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

Collaborations: We have increased collaboration with two community ALFs and the Council on Aging of Northwest Florida.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

Fiscal Year 2020-2021 Closed Grants
(Funding Year 2017-2018)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
8AZ03	Florida Institute of Technology	Yi Liao, PhD	$ 100,000	08/31/2020	No	Yes	Yes
8AZ05	Florida State University	Henry J Carretta, PhD, MPH	$ 100,000	02/28/2020	No	No	No
8AZ06	Mayo Clinic	Melissa E. Murray, PhD	$ 221,000	02/28/2021	No	Yes	No
8AZ07	Mayo Clinic	Chia-Chen Liu, PhD	$ 221,000	02/28/2021	No	Yes	No
8AZ08	Mayo Clinic	John A. Lucas, PhD	$ 200,000	08/31/2021	No	Yes	Yes
8AZ13	University of Central Florida	Florencio Hernandez, PhD	$ 200,000	08/31/2020	No	No	No
8AZ15	University of Florida	Kesavalu Lakshmyya BVSc,MSc,SCC	$ 221,000	08/30/2020	No	No	No
8AZ17	University of Florida	Linda B. Cottler, PhD, MPH, FACE	$ 200,000	02/28/2021	Yes	Yes	No
8AZ22	University of Miami	Noam Alperin, PhD	$ 221,000	02/28/2021	No	Yes	No
8AZ23	University of Miami Miller School of Medicine	David Loewenstein, PhD	$ 450,844	02/28/2021	No	Yes	Yes
8AZ29	University of South Florida	David E. Kang, PhD & Jung A. Woo, PhD	$ 221,000	08/31/2020	No	Yes	No
8AZ32	The Roskamp Institute	Andrew P. Keegan, MD	$ 99,526	08/31/2020	No	No	No

1. **Grant #:** 8AZ03 Carbon Monoxide Releasing Polymer Nanoparticles for Treatment of Alzheimer's Disease

Principal Investigator: Yi Liao, PhD

Organization: Florida Institute of Technology

Abstract: The goal of this project is developing brain-delivery polymer nanoparticles loaded with carbon monoxide (CO) releasing molecules (CORMs) for studying the CO effects on Alzheimer disease. The research team made two major acheivements:

1. Development of a new synthetic method for preparing and modifying polybutylcyanoacrylate (PBCA), which is a brain delivery polymer. Also developed was a new photo-carbon monoxide (phtoCORM) releasing molecule. Bacteriophage DK4 was then encaosulated in PCBA nanoparticle. The study showed that the nanoparticle has low cytotoxicity and releases CO nearly quantitatively under visible light. An article about this work was published in Photochemistry and Photobiology Science as the front cover of the issue.

2. Previous studies have shown that ultrasound can open the blood-brain barrier and thus allow drugs to be delivered to brain. Therefore, ultrasound responsive nanoparticles containing CORMs have been studied. One of the CORMs used was CORM2, which releases CO in the presence of some amino acids and proteins. CORM2 has shown many therapeutic effects including anti-inflammation and neuro-protecting effects in previous studies. Nanoparticles of pluronic, a Food and Drug Administration proved drug delivery polymer, and CORM2 were prepared and studied. Results showed that the CORM-2 in the nanoparticle was effectively activated by ultrasound. This is a breakthrough since no ultrasound responsive CO releasing

material has been reported before. This team has filed an invention disclosure form for this discovery. This project is a collaborative project of the principal investigator (PI) (Dr. Liao) and co-PI (Dr. Wehmschulte). The team will continue our collaboration to develop novel carbon monoxide releasing materials and methods. During the project, the team established collaboration with Dr. Bashur, Dr. Copik, and Dr. Kanekiyo, known experts in vascular disease, immunotherapy, and neurological diseases respectively. In the future, the team will continue our collaboration to apply the carbon monoxide releasing materials developed by our group to these areas. Especially, the ultrasound CORM release studied in the project is both novel and has translational potential, and thus is expected to generate promising results in near future. The team will use the preliminary results of these collaborative work to apply funding from National Institute of Health, National Sanitation Foundation, and Florida Department of Health etc.

Follow-on Funding: Effects of CO on the vascular cognitive impairment and dementia. Community Foundation of Brevard. Chris Bashur. $26,000.

Collaborations: This project is a collaborative project of the PI (Dr. Liao) and co-PI (Dr. Wehmschulte). During the project, we have established collaboration with Dr. Bashur at Florida Insititute of Technology, Dr. Copik at University of Central Florida, and Dr. Kanekiyo at Mayo Clinic, who are experts in vascular disease, immunotherapy, and neurological diseases respectively.

Journals: Poly(butyl cyanoacrylate) nanoparticle containing an organic photoCORM. A Elgattar, K S. Washington, S Talebzadeh, A Alwagdani, T Khalil, O Alghazwat, S Alshammri, H Pal, C Bashur and Y LiaoPhotochemical & Photobiological Sciences. 2019.

Patents: None at the time of reporting.

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

Principal Investigator: Henry J. Carretta, PhD, MPH

Organization: Florida State University

Abstract: Health Services Research using administrative claims is not known for finding "significant scientific accomplishments" early in the program of research. Rather, it begins with a series of iterative steps to extract the data of interest from a larger data set leading to the creation of smaller set of data records and variables for analytic purposes. In the case of this project, the starting point was national fee-for-service Medicaid claims for 2008-2010. Each calendar year from 2008-2010 includes about 40 million persons and 100's of millions of individual claims grouped into six categories.

The goal being to create Florida specific files that includes only individuals and variables of interest to this study. It is not unusual for this type of study to devote most of the time and resources to getting to the point where actual analysis can begin. The staff began with the national FFS Medicare claims data for 2010. These records are provided as six separate files. The annual patient summary or Denominator file and five separate claims files organized by source of care. The Denominator includes summarized enrollment information and demographic characteristics for each beneficiary. This is structured as one record for each person enrolled in Medicare Part A, Part B and/or C during that calendar year. Any beneficiaries with one or more

months in Part C (private insurance managed care plans) were excluded as no claim or encounter records are provided for that group in 2010. A small number of beneficiary records are excluded if the race or sex variables are recorded as missing or unknown. Hispanic ethnicity is included as a race category rather than a separate variable. As a result, it is not possible to identify white Hispanics versus non-Hispanic. Races other than White, Black and Hispanic were excluded to focus on the Black and Hispanic versus White differences and disparities.

Beneficiaries with a recorded age less than or equal to 64 at the end of 2010 were excluded. Beneficiaries were excluded if their state of residence was not listed as Florida. Additional Florida residents were excluded if the Social Security Administration county codes in the Denominator file were missing were not one of the 67 codes associated with real Florida counties.

The remaining five file types have FFS claims records for inpatient hospital, outpatient hospital, skilled nursing care, professional services, and home health care. The professional services file (physicians and other provider types) is a 5% sample of all Medicare FFS beneficiaries in 2010. The other source files are 100% samples of the annual FFS claims by beneficiary for each source type. The size of the professional services file prevents Medicare from distribution of a 100% professional services file to researchers. These are structured as one or more claims per beneficiary and can be linked to the Denominator file. Variables were created in this file that created yes/no indicators for Alzheimer's Disease Research Center (ADRC) patients, various comorbid chronic conditions, death during 2010 and utilization associated with the five source file types. Other variables were also recode into convenient categories and groups. Additionally, the 2008 and 2009 calendar year files were searched for beneficiary id numbers that appeared in the 2010 file. They were included as 2010 cases if they appeared in the 2010 denominator file, utilized services in 2010, but did not have any ADRC diagnosis codes in 2010 claims. Case definitions are based on the Centers for Medicare and Medicaid Services (CMS), Chronic Condition Warehouse case definitions for 27 conditions. Preparation of these files for analysis was completed in the fall of 2019. The immediate goal is to finish the analysis and publish a paper on this research and its findings.

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.

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

Principal Investigator: Melissa E. Murray, PhD

Organization: Mayo Clinic

Abstract: The Ed and Ethel Moore Alzheimer Research grant mechanism has enabled us to maintain the FLorida Autopsied Multi- Ethnic (FLAME) cohort. Utilizing our preliminary data and funded effort over the last two years we have successfully gathered important demographic, clinical, and neuropathologic information. The team has utilized the FLAME cohort to publish

three publications centered on Alzheimer's disease from the perspective of ethnoracial differences, age and sex interactions, and hippocampal vulnerability. The team participated in an important perspective regarding ethnoracial disparities through a collaboration with colleagues organized by the Alzheimer's Association. The impact of COVID-19 greatly limited our ability to work in the laboratory, but we were able to continue to disseminate important information to the scientific community through three high-impact review articles on atypical (non-memory forms) of Alzheimer's disease, selective vulnerability of the locus coeruleus, and a deep examination on neurofibrillary tangle maturity. To ensure continued transcriptomic investigation of the memory center (hippocampus) in Alzheimer's disease (Crist et al., Nature Communications 2021) is broadly applicable, the team has secured additional funding through the Ed and Ethel Moore Alzheimer Research grant mechanism (20A22). It is important to ensure that the State of Florida autopsy program is being better utilized by underrepresented minorities. I would like to further discuss options for ensuring any aspect of financial burden is not put on families with regard to the autopsy program, which may negatively impact participation in low income families.

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

Collaborations: None at the time of reporting.

Journals: Selective Vulnerability of the Nucleus Basalis of Meynert Among Neuropathologic Subtypes of Alzheimer Disease. Hanna Al-Shaikh F.S., Duara R. Crook J.E., Lesser E.R., Schaeverbeke J., Hinkle K.M., Ross O.A., Ertekin-Taner N., Pedraza O., Dickson D.W., Graff- Radford N.R., Murray M.E. JAMA. 2020.

Visualization of neurofibrillary tangle maturity in Alzheimer's disease: A clinicopathologic perspective for biomarker research. Moloney C.M., Lowe V.J., Murray M.E. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2021.

Transcriptomic analysis to identify genes associated with selective hippocampal vulnerability in Alzheimer's disease. Crist A.M., Hinkle K.M., Wang X., Moloney C.M., Azu N.O., Frankenhauser I., Labuzan S.A., Matchett B.J., Liesinger A.M., Lesser E.R., Serie D., DeTure M., Tang X., Petersen R.C., Duara R., Graff-Radford N.R., Allen M., Carrasquillo M.M., Li H., Ross O.A., Ertekin-Taner N., Dickson D.W., Asmann Y.W., Carter R.E., Murray M.E. Nature Communications. 2021.

The mechanistic link between selective vulnerability of the locus coeruleus and neurodegeneration in Alzheimer's disease. Matchett B.J., Grinberg L.T., Theofilas P., Murray M.E. Acta Neuropathologica. 2021.

Patents: None at the time of reporting.

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

Principal Investigator: Chia-Chen Liu, PhD

Organization: Mayo Clinic Jacksonville

Abstract: The goal of the study is to examine how Alzheimer's Disease (AD)-associated triggering receptor expressed on myeloid cells-2 (TREM2-R47H) mutation affects microglial

functions and amyloid development *in vivo*. The study team generated TREM2 inducible mice expressing TREM2 WT or R47H. After breeding to Cx3cr1- CreER mice, TREM2 was specifically expressed in the microglia upon tamoxifen induction. In the first year, the team established the experimental animals in the absence of amyloid pathology. Researchers characterized the animal cohort and demonstrated the functionality of the animal models upon tamoxifen induction. The study team examined hTREM2, and specific microglia-related genes (such as Tyrobp, Aif1, Hexb, C1qa, C1qb, Csf1r, cd33 and cd68, etc.) by real-time Polymerase Chain Reaction. hTREM2 expression was upregulated in both TREM2 wild type (WT) or TREM2-R47H mice, confirming the expression of TREM2 in the mouse models and effects on microglia-specific gene expressions. To examine how TREM2 WT or R47H affect microglial function, scientists examined the microglial morphologies, including the numbers of processes and branches as well as the size of the microglial cell body in TREM2 WT or TREM2-R47H mice. Significantly, the team further demonstrated that microglia from TREM2-R47H mice exhibited similar soma size but had less branches and junctions of the processes compared with TREM2 WT microglia. These results indicate that the microglial carrying TREM2 R47H variant may exhibit distinct functions compared with wildtype microglial. In addition, the team examined the cognitive function (ie., LTP) of experimental mice by electrophysiology. The study team found that TREM2-WT expression is capable of increasing synaptic function, but R47H failed to do so. These results suggest that R47H is a loss-of-function mutation which causes an impairment of microglial function to support synapses. Scientists also explored the potential mechanisms by which TREM2-WT and TREM2-R47H microglia affect brain function using RNA-sequencing (24 mouse samples from 4 groups: Ctrl-WT, TAM-WT, Ctrl-R47H and TAM-R47H). From this analysis, the circadian behavior and circadian regulation of gene expression and circadian sleep/wake cycle were significantly changed in TREM2-R47H mice compared with control mice. Network analysis demonstrated that the metabolic process, transcription factor activity, Deoxyribonucleic acid (DNA) binding and regulation, etc. were down-regulated in TREM2-R47H mice, but not in TREM2-WT. These results indicate that TREM2-R47H may disrupt the circadian regulation and regular metabolic pathways in microglia.

To investigate the effects of WT and R47H on amyloid pathogenesis, the study team bred our animal models with 5xFAD amyloid model mice. Researchers designed three paradigms to investigate the specific effects of TREM2-WT or TREM2- R47H on amyloid deposition: first, during the Aβ seeding (0-3.5 month); second, during rapid growth period (2-5 month); third, during saturation stage (5-8 month). Importantly, the team showed that the expression of TREM2-WT at 0-3.5 month (in the Aβ seeding stage) significantly reduced the total amyloid plaque burden, whereas expression of TREM2-R47H did not have significant effect on amyloid deposition, whereas expression of TREM2-R47H did not have significant effect on amyloid deposition. Consistent with the results from the immunostaining, expression of TREM2-WT reduced Abeta levels, but expression of TREM2-R47H had no effect on the insoluble Aβ. To assess the effects of TREM2 on plaque- associated dystrophic neurites, a key pathological feature of AD, scientists performed immunostaining with an antibody against the lysosome-associated membrane protein 1 (LAMP1), which typically accumulates in damaged neurites. Consistent with the amyloid burden, a significant reduction of dystrophic neurites when TREM2-WT was expressed during the early Aβ seeding stage. In addition, the team examined the TREM2 effects during the amyloid development stage. The induction of TREM2 expressions were performed in mice at two months of ages, and the animals were harvested at five months of age. Interestingly, researchers found that amyloid plaque numbers as well as fibrillar amyloid plaque were significantly higher in FAD mice expressing TREM2-R47H compared with littermate

controls, whereas expression of TREM2-WT had no significant effects on amyloid deposition. Scientists are in the process of examining the late-stage cohorts. Overall, the findings indicate that TREM2 plays a critical role in modulating microglial function and amyloid deposition. In addition, their functions were distinct at different stages of amyloid development which dramatically influence AD pathology. Researchers expect to complete the project in the next few months and publish our findings. Since TREM2 affects microglia functions which modulate circadian behavior and circadian regulation in mice, researchers plan to further examine how TREM2-WTand R47H expression in microglia affect neuronal activity. Also, scientists plan to explore the effects of TREM2 on tau-mediated pathogenesis and neurodegeneration.

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

Collaborations: None at the time of reporting.

Journals: Vascular ApoE4 Impairs Behavior by Modulating Gliovascular Function. Yu Yamazaki, Chia-Chen Liu, Akari Yamazaki, Betty Y.S. Kim, Takahisa Kanekiyo, Guojun Bu. Neuron. 2021.

Patents: None at the time of reporting.

5. **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

Abstract: This community-based, participatory research project collected dementia-specific community health needs assessment data using resources modified from the National Association for Providers of Activities for older people (NAPA) Dementia Friendly America toolkit. These data were used to inform the development of a Dementia Friendly Community (DFC) project in a neighborhood of Jacksonville, FL located in a region with a high African American population (96%) and the highest rates of health-related disparities in the city. The overall goals of the project were to increase community awareness of dementia and improve quality of life of African Americans with memory loss, mild cognitive impairment (MCI), Alzheimer's disease (AD) and AD related dementia (ADRD) and their loved ones/caregivers. The scientific aims of the study were to measure the impact of the DFC model on dementia knowledge scores, caregiver burden, and knowledge of community resources for people with dementia and their loved ones. The study team hopes to continue to leverage the partnerships and infrastructure developed under this grant to engage African American community members into longitudinal studies of aging and dementia, including a study of barriers to brain donation research which is currently under grant review. The study team has also begun leveraging the programs developed under this grant to engage nearby communities with a goal of expanding the "Dementia Friendly" outreach model to a larger catchment area in the Jacksonville African American community. The researchers have also obtained pilot funding to apply lessons learned from this project to the development of dementia outreach to local Hispanic communities.

Follow-on Funding: Pressing Toward the Mark: A Faith-Based Approach to Dementia Education. Community Foundation of Northeast Florida. M. Robinson. $20,000.

Between Here and There: Addressing End-of-Life Disparities Among African Americans with MCI and Dementia Through Community-Based Training in Advance Care Planning. FLDOH. M. Robinson. $270,000.

Development of a Memory Café in an African American neighborhood. Community Foundation of Northeast Florida. J. Lucas. $13,000.

Core E: Outreach, Recruitment & Engagement. Mayo Clinic Alzheimer's Disease Research. NIA. J. Lucas. $815,000.

LEADing Diverse Recruitment for the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS). Alzheimer's Association. Gregory Day, MD. $124,472.

Collaborations: Through this project, researchers have developed or deepened community partnerships with the Alzheimer's Association, FL DOH Dementia Care and Cure Initiative, Edward Waters University Health Disparities Center, Community Hospice, and Community Foundation of Northeast Florida. The work performed under this activity contributed to the selection of Dr. Lucas (PI) to serve on the Florida SHIP PA9-1.1 (Establish FL DOH as a COE pursuant to the federal BOLD Infrastructure for Alzheimer's Act). In the final year of the grant, we partnered with the Mayo Clinic Center on Health Equity & Community Research to transition programs developed under this grant to commuity ownership.

Journals: Approach to Alzheimer's disease education in two African American neighborhoods. Bergeron, Robinson, Willis, Lucas. Journal of Ethnic and Racial Disparities. 2021.

Patents: None at the time of reporting.

6. **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

Abstract: This project will combine two-photon circular dichroism (TPCD) and isotope-edited Fourier transform infrared (IE-FTIR) spectroscopy to elucidate the structural details of full-length A peptide and several fragments that represent structurally distinct and functionally important stretches of the peptide. In addition, membrane pore formation by A and its fragments will be studied by fluorescence spectroscopy and a relationship between peptide structure and its pore forming activity will be established. The unsurpassed sensitivity of TPCD to small structural distortions and its capability to access specific fingerprints in a region of the electromagnetic spectrum inaccessible by any other means (vacuum ultraviolet-VUV), combined with the characteristic site-specific resolution and sensitivity of IE-FTIR to small differences in intra- and interstrand H-bonding in -sheets, guarantee the access to specific structural distinctions between highly neurotoxic (A11-28, A25-35 and A1-42) and mildly toxic (A1-40) A. The results will identify the specific structural features of the four peptides that are related to most potent membrane pore forming capabilities, which will a) lead to structural models for the pores, b) relate peptide cytotoxicity to its structure, and c) elucidate the molecular mechanism A-beta toxicity.

The first major findings have been the unexpected hairpin like conformation of Ab25-35, the presence of a strong out-of-plane dipole moment, and the stabilization of dimers and trimers in anti-parallel configuration, in vacuo and in water. Based on these data, two papers have been published: 1. Kandel et al. Sci. Rep. 9(1):2689, 2019; 2. Tatulian and Kandel Methods Mol. Biol. 2003, 449-464, 2019.

Researchers oberved that monomers preserve their L-S shape topology in all oligomers, and that protofibrils in antiparallel arrangements present a strong dipole moment virtually aligned in the direction of the structure axis.

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.

7. **Grant #:** 8AZ15 Periodontal Bacteria Augment Progression of Aβ and Tau Pathology

Principal Investigator: Kesavalu Lakshmyya BVSc,MSc,SCC

Organization: University of Florida

Abstract: Researchers bred APP (Amyloid precursor protein) TgCRND8 transgenic (tg) [APP (swe/ind), CRND8] and nontransgenic (ntg) mice and initiated Specific Aim I study to Investigate the role of Treponema denticola in regulating of Aβ plaque pathology in TgCRND8 mouse model of Alzheimer's disease-like amyloidosis. The research team conducted this study in two batches as the transgenic mice breeding yield is low (30-40%) and also sudden death syndrome is high (50- 60%).

In specific Aim I experiment, the animals were infected orally with T. denticola and Streptococcus gordonii bacteria for 6 infection cycles. At the end of the experiment, researchers found bacterial colonization (T. denticola and S. gordonii) in oral cavity of transgenic and non-transgenic mice which was confirmed through colony polymerase chain reaction (PCR) technique using 16S ribosomal ribonucleic acid (rRNA) bacteria-specific primers. In addition, scientists measured alveolar bone resorption (ABR) in sham-control and bacteria-infected groups. The horizontal ABR was significantly increased (P<001) in bacteria-infected (Tg, nTg) mice compared to sham-infection in Tg and nTg mice. Tg and nTg CRND8 mice infected with T. denticola or S. gordonii were shown positive for DNA in oral plaque samples (100%), brain, heart, lung, liver, spleen, and kidney tissues. Further, Sanger dioxynucleic acid (DNA) sequencing technique confirmed the presence of T. denticola in the mice brain. The results of Immunofluorescence (IF) microscopy analysis of T. denticola in mouse brain tissue showed T. denticola morphology in mouse brain cortex region of T. denticola-infected group. The immunohistostaining showed a higher number of activated astrocytes and significant expression (P<001) of astroglial marker GFAP in the brain cortex and hippocampus was observed in both Tg and nTg CRND8 mice infected with T. denticola or S. gordonii of TgCRND8 mice infected with T. denticola and S. gordonii.

Similarly, specific Aim II experiment was performed: The researchers have done intracranial infection of six groups of mice by six batches to demonstrate whether oral spirochete T.

denticola directly injected into the brain can seed amyloid deposition in TgCRND8 mouse model of AD-like amyloidosis. The data analysis for this study are under progress. In addition, a pilot study has been performed to confirm the presence of live bacteria (T. denticola) after intracranial infection in the brains of the TgCRND8 and non-transgenic mice at different time intervals (1, 4, 8 and 24 hours). We have found viable and motile spiral-shaped spirochete cells at all the time points (1, 4, 8 and 24 hours). Further, the results of PCR analysis with T. denticola specific 16S rRNA gene amplification and Sanger DNA sequencing confirmed that the isolated pure bacterial culture as T. denticola. Due to COVID-19 pandemic, University of Florida (UF) shut down all research activities including animal care services and all research laboratories in late March 2020. Following University of Florida Research Resumption Plan, the principal investigator's laboratory was reopened in June 1 2020 in staged manner. We started analyzing the pending tissue analysis. The research personnel were not allowed to perform research at collaborators Drs. T.E. Golde and Yona Levites laboratory in CTRND Neuroscience due to COVID-19 laboratory regulation.

This study reports will be used as a basis for future research studying Alzheimer's disease (AD) neurofibrillary tangles tau pathology in brain upon oral microbial infection (Mono- and polymicrobial infection). In addition, the role of multiple species infection (polymicrobial infection) in amyloid β and tau pathology will be studied in detail using other amyloid-β and tau animal model systems.

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 #:** 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

Abstract: The "Precision Public Health Approaches to Reduce Disparities in Memory Disorder Screening in Rural Minority Communities " program was able to extend its reach and impact through the use of a Community Health Worker (CHW) model that provides a health intake, Alzheimer's disease (AD) questionnaire and Montreal Cognitive Assessment (MoCA) for older adults in North Central and Northwest Florida; information and educational materials provided to older adults and their caregivers about memory disorders and AD through CHWs; distribution of a continuing medical education (CME) video for primary care and internal medicine clinicians serving those living in rural counties in North Central and Northwest Florida; and, recruitment of and training of additional Community Health Workers to serve older adults in the targeted counties.

The CHW model of engagement with older adults resulted in the enrollment of 586 older adults in this project. Older adults were recruited in target counties Alachua, Marion, Putnam, Calhoun, Jackson, and Bay as well as additional counties in Florida where older adults may benefit from

cognitive screening. The CHWs conducted a consent process with older community members at the end of which the community member could consent to participate in a health assessment to better understand their health conditions. After the assessment was completed, the CHW reviewed it and, then, on the basis of extensive knowledge of community resources, connected older adults to social and medical services in the community. As of December 2020, CHWs provided 1,271 referrals to older adults through this project. The CHWs also conducted an AD questionnaire and Montreal Cognitive Assessment (MoCA). The older adults, and when possible, their caregiver(s), were also given educational information about AD. The CHW model included information, education, connections to local social and medical services, and follow-up calls at 60 and 120 days.

The research team continues 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. 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: Florida State University (FSU; Tallahassee, FL), Florida Blue and the UF Clinical and Translation Science Institute:Collaboration continues with our CTSI, which includes FSU and UF, to meet workforce needs, to help monitor the project (our CTSI Community Advisory Board), and to encourage participation in the CME. We coordinated our work with Dr. Joedrecka Brown, Dr. Jessica De Leon, and Dr. Lisa Gardner.

University of Florida, College of Public Health and Health Professions/College of Medicine, Department of Epidemiology, Gainesville FL:The Department of Epidemiology is responsible for the oversight and coordination of all aspects of the project. Dr. Linda Cottler is the principal investigator of the project. She is currently the Associate Dean for Research for the College of Public Health and Health Professions and Dean's Professor in the Department of Epidemiology. Dr. Catherine Striley is a co-investigator on the project. She is a Research Associate Professor in the Department of Epidemiology. Pre-doctoral student Shawnta Lloyd is the Project Coordinator for the project.

University of Florida, HealthStreet, Gainesville FL: HealthStreet employs CHWs who go into the community to recruit and enroll community members into the project. CHWs meet community members where they live, work, and recreate to recruit potential members. CHWs are responsible for administering the HealthStreet intake which assesses medical history, medical concerns, and willingness to participate in research. In addition, CHWs administer the AD knowledge questionnaire and the MoCA to assess cognitive health in community members. Community members who receive a score of less than 26 on the MoCA are referred to their primary physician by the CHW. HealthStreet provides training to CHWs. An online distance learning platform has been developed to ensure high quality training for the new CHWs and volunteers. This distance learning platform allows our program to reach all parts of the state and ensures the fidelity of the model. After the completion of online training, a senior CHW at UF HealthStreet and a faculty member in the Department of Epidemiology certify new CHWs and confirm their readiness to enter the field. As a final step in training, a senior CHW from HealthStreet travels to the county in which the CHW will recruit older community members. The

new CHW has the opportunity to shadow the senior CHW and enhance their familiarity with the intake process. This method of shadowing is beneficial to the new CHW as it allows the CHW to observe and participate in the successful recruitment of older adults in their own communities.

Alzheimer's Association: Staff continue to collaborate with Deann Marasco (Director, Health Systems, State of Florida, Alzheimer's Association) and Audrey Coachman (Program Manager, Alzheimer's Association, Central and North Florida Chapter) to increase screening and knowledge of dementia in underserved areas in central and northwestern Florida.

Northwestern Florida Partnerships: Clinical and Translational Science Institute (CTSI) affiliated faculty at Florida State University (as above), WYBT AM 1000 Radio, The University of Florida's Institute of Food and Agricultural Sciences (UF/IFAS), Blountstown Library, Jackson County Libraries, Jackson County Senior Citizens Center, Calhoun County Senior Citizens Center, New Direction Christian Center,

Marion County Partnerships: Seven Senior Nutrition meal sites: Belleview, Dunnellon, Flemington, Forest, Marion Café, Marion Oaks, Sparr, Barbara Gaskin Washington Adult Activity Center (for Seniors), Eighth Avenue Adult Activity Center (for Seniors), Marion County Libraries

Putnam County Partnerships: Food Pantries: Heart of Putnam Food Pantry, St. Andrews Food Pantry, Barry Manor Meal Site- senior meal site, First Baptist Church Farmshare, First, Presbyterian Church, Putnam Housing Authority, Putnam Christian Services, American Legion, Hitchcock's Markets, Interlachen Soup Kitchen, Melrose Senior Center (serves some from Putnam County)

Journals: Journal of Immigrant and Minority Health. Otufowora A, Liu Y, Young H, Egan KL, Varma DS, Striley CW, Cottler LB. Sex differences in willingness to participate in research based on study risk level among a community sample of African Americans in North Central Florida. 2020.

The association between emergency department super- utilizer status and willingness to participate in research. Young HW, Martin ET, Kwiatkowski E, Tyndall JA, Cottler LB. Emergency Medicine International. 2020.

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Correlates related to follow-up in a community engagement program in North Central Florida. Otufowora A, Liu Y, Varma DS, Striley CW, Cottler LB. Journal of Community Psychology. 2020.

Patents: None at the time of reporting.

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

Principal Investigator: Noam Alperin, PhD

Organization: University of Miami

Abstract: The project assessed and quantified the effect of poor sleep quality and cerebral vascular disease on cognitively critical brain regions which are involved in the pathophysiology of dementia of the Alzheimer disease (AD) type. It has been well documented that poor sleep quality is strongly associated with AD. However, it has not been widely investigated how poor sleep impacts elderly subjects who are not demented (i.e., cognitively normal). Researchers studied the effect of poor sleep in normal elderly community-dweller subjects ages 60 to 80 years and found that poor sleep has a significant negative impact on brain health. Compared with good sleepers, poor sleepers have significantly smaller cognitively critical brain regions (e.g., hippocampus, superior parietal lobules, and the amygdala), on the order of 7% smaller volumes. This important finding was published in 2019 in the main sleep journal. This finding implies that sleep intervention should be considered well prior to onset of cognitive decline in order to slow down progression to dementia. Secondly, the study team further investigated which sub-regions of the hippocampus (i.e., hippocampal subfields) were smaller in the poor sleepers and found two regions that are significantly impacted in the poor sleepers. This finding has been recently accepted for publication in the journal Sleep Research. The plan is to investigate the mechanism by which poor sleep impacts brain health. The team is now investigating the role of the Cerebral Spinal Fluid (CSF) flow dynamics on the efficacy of removal of the brain toxins. It was discovered that the CSF movement between the brain and spine is 2.5 folds higher is the supine posture compared to the upright posture.

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

Collaborations: None at the time of reporting.

Journals: Effect of Sleep Quality on Hippocampal Subfields in Cognitively Normal Elderly Individuals. Liu C, Lee SH, Loewenstein D, Hernandez- Cardenache R, Alperin N. Sleep Research. 2021.

Patents: None at the time of reporting.

10. **Grant #:** 8AZ23 The Relationships Between Multimodal Neuroimaging Biomarkers and Novel Cognitive Stress Tests Among Ethnically Diverse Older Adults

Principal Investigator: David Loewenstein, PhD

Organization: University of Miami Miller School of Medicine

Abstract: This research study has assembled a unique consortium between top investigators from the University of Miami, University of Florida, Florida International University and Mount Sinai Medical Center and provided 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 (AD) among diverse ethnic and cultural groups (African-American, Hispanic and White-Non-Hispanic) at risk for AD; b) employing study state-of-the-art multi-modal neuroimaging (tau PET/CT, amyloid PET/CT, Brain MRI to measure cortical thickness, regional brain volumes, and DTI).

This consortium of experienced and productive investigators was the first in the state of Florida to examine the relationship between the CST, tau and amyloid load in the brain as they relate to cognitive markers that have been found to be sensitive to detecting preclinical AD by uniquely tapping susceptibility to proactive semantic interference (PSI) and failure to recover from PSI

(frPSI), and failure to recover from retroactive semantic interference frRSI. 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 recruited additional diverse older adults at risk for early AD.

This collaborative study was of high impact and expanded early detection of preclinical AD and emerging treatments. It will also yield important and critical pilot data that led to the funding of a successful collaborative R01 award from the National Institutes of Health/National Institute on Aging.

Life Molecular Imaging (formerly Piramel) has provided the study team with a tau reagent to image a subset of 30 participants. This study represents the first attempt in the country to relate these novel cognitive markers associated with amyloid to tau in the brain. The tau imaging infrastructure at the University of Miami was built due to this award and continues in operation under the federally funded award. Follow-on funding was achieved through a federally funded R01 grant award by the NIH/NIA awarded to PI Loewenstein in the amount of ~2.6 million dollars to further study the relationship of cognitive performance on the CST with tau imaging. 1 R01 AG061106-01 Title: A Novel Computerized Cognitive Stress Test Designed for Clinical Trials in Early Alzheimer's: Relationship with Multimodal Imaging Biomarkers in Diverse Cultural Groups.

Follow-on Funding: A Novel Computerized Cognitive Stress Test Designed for Clinical Trials in Early Alzheimer's: Relationship with Multimodal Imaging Biomarkers in Diverse Cultural Groups. National Institute on Aging. David A Loewenstein. $2,206,617.

Collaborations: None at the time of reporting.

Journals: Mild Cognitive Impairment is Characterized by the Inability to Recover from Proactive Semantic Interference across Multiple Learning Trials. Loewenstein, DA Curiel- Cid, RE, Kitaigorodsky, M, Crocco, EA, Zheng, DD, Gorman, KL. The Journal of Prevention of Alzheimer's Disease. 2021.

Patents: None at the time of reporting.

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

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

Organization: University of South Florida

Abstract: The specific aims of this proposal are to determine the role of RanBP9 complexes on tau aggregation and microtubule dynamics; directly test the effect of cofilin activation status on tauopathy *in vivo*. The study team has made significant progress on the proposal. Researchers tested whether RanBP9 complexes affect tau oligomers as we confirmed RanBP9 per se promotes tau aggregation. Obtained tau oligomeric antibodies and tested whether RanBP9/Hsc70/Hsp90 complexes affect tau oligomers. Scientists have found that RanBP9 partially interferes with tau-induced microtubule stability and stabilizes tau levels at least in part by promoting tau deubiquitination. A manuscript was published in Communications biology in March 2019, including a recently published review paper on the role of cofilin as a masternode regulating the cytoskeletal pathogenesis of Alzheimer's Disease (AD) in the Journal of

Alzheimer's Disease. The researchers have also been working on the dual role of cofilin in APP trafficking and Abeta metabolism, which was recently published in the FASEB journal, including a published paper in Autophagy describing the role of SSH1, a cofilin activating enzyme, in promoting tauopathy via an autophagy pathway. Based on this work on RanBP9, the study team found that RanBP9 interacts with the ubiquitin specific peptidase USP11 and enhances USP11-tau complex formation. This results in tau deubiquitination and increased tau levels. Scientists are currently working to validate this hypothesis *in vivo*.

Follow-on Funding: Deubiquitinase USP11 in tau regulation and age-related tauopathy. NIH/NIA. Kang, David & Woo, Jung A. $1,868,750.

Collaborations: None at the time of reporting.

Journals: CHCHD10-regulated OPA1-mitofilin complex mediates TDP-43-induced mitochondrial phenotypes associated with frontotemporal dementia. Liu T, Woo JA, Bukhari M, LePochat P, Chacko A, Selenica M, Yan Y, Kotsiviras P, Cazzaro S, Zhao X, Kang DE. Faseb Journal. 2020.

SSH1 impedes SQSTM1/p62 flux and MAPT/Tau clearance independent of CFL (cofilin) activation. Fang, C. Woo, J.A., Liu, T. Zhao, X., Cazzaro, S., Yan, Y., Matlack, J., Kee, T. LePochat, P., Kang, D.E. Autophagy. 2020.

Patents: None at the time of reporting.

12. **Grant #:** 8AZ32 Longitudinal Assessment of Brain Derived Neurotrophic Factor Levels with Bacopa Monnieri Treatment in Those at Risk of Developing Alzheimer's Dementia

Principal Investigator: Andrew P. Keegan, MD

Organization: The Roskamp Institute

Abstract: During the first year of this project, the goal was to collect clinical data and blood samples from subjects who have been visiting annually for memory assessments. This portion has been completed and blood samples have been analyzed and we are working with our statistician on preparing a manuscript submission. The second portion of the project has also been completed. Researchers successfully collected and analyzed blood samples of subjects before and after they took a supplement (Bacopa) for three months.

There were no significant changes in key personnel, scientific programs, shared resources or institutional commitments. This research has established a basis to further develop our understanding of Brain Derived Neurotrophic Factor (BDNF) and it's meaning in memory risk. We plan to look for future funding to better delineate the underlying pathways that could be explain our findings. The study team also plans to obtain some preliminary data in another disease state, Multiple Sclerosis. This grant also established a collaboration with Swinburne University in Australia and there are plans for future collaborations that stem from this project. The primary goal, however, is to secure follow-on funding.

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

Collaborations: The current grant led to a collaboration with an Australian professor, Dr. Con Stough. Since the initiation of this grant, Dr. Stough visited the Institute and researchers have begun talks on future projects/collaborations that may involve international clinical trials.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

Fiscal Year 2020-2021 Closed Grants
(Funding Year 2016-2017)

Grant #	Organization	Principal Investigator	Award Amount	End Date	Patents	Publications	Follow-on Funding
7AZ11	University of Central Florida	Kiminobu Sugaya, PhD	$ 100,000	03/31/2021	No	No	No
7AZ22	Mayo Clinic	Takahisa Kanekiyo, MD, PhD	$ 250,000	03/31/2021	No	Yes	Yes
7AZ26	University of Miami Miller School of Medicine	Claes Wahlestedt, MD, PhD	$ 100,000	03/31/2021	No	No	No

1. **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

Abstract: Finally, studies of the dynamics of the aggregation process of Ab1-42 via dipole-dipole interaction supported the cascaded-polymerization mechanism via dipole interaction. This is perhaps the most relevant result for it opens a new understanding of the predominant mechanims of action 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.

2. **Grant #:** 7AZ22 APOE and Cerebrovascular Aging in Alzheimer's Disease

Principal Investigator: Takahisa Kanekiyo, MD, PhD

Organization: Mayo Clinic

Abstract: In order to accomplish our goals we have combined linear spectrocopy (UV-vis and ECD) and theoretical calculations at the hartree-Fock level, as well as performing semi-empirical calculations and molecular dynamics at the PM6 level. Based on these data, one paper has been submitted for publication to ACS Omega. Additionally, researchers have made five different presentations in national and international conferences.

Follow-on Funding: NIH/NIA. Takahisa Kanekiyo. $1,173,750.

Collaborations: None at the time of reporting.

Journals: Apolipoprotein Ein Brain Pericytes Regulates Endothelial Function in an Isoform-Dependent Manner by Modulating Basement Membrane Components. Yamazaki Y, Shinohara M, Yamazaki A, Ren Y, Asmann YW, Kanekiyo T, Bu G. Arterioscler Thromb Vasc Biol. 2020. Jan;40(1):128-144. doi: 10.1161/ATVBAHA.119.313169.

Selective loss of cortical endothelial tightjunction proteins during Alzheimer's disease progression. Yamazaki Y, Shinohara M, Shinohara M, Yamazaki A, Murray ME, Liesinger AM, Heckman MG, Lesser ER, Parisi JE, Petersen RC, Dickson DW, Kanekiyo T, Bu G.Brain.2019 Apr 1;142(4):1077-1092. doi: 10.1093/brain/awz011.

Tau and apolipoprotein E modulate cerebrovascular tight junction integrity independent of cerebral amyloid angiopathy in Alzheimer's disease. Liu CC, Yamazaki Y, Heckman MG, Martens YA, Jia L, Yamazaki A, Diehl NN, Zhao J, Zhao N, DeTure M, Davis MD, Felton LM, Qiao W, Li Y, Li H, Fu Y, Wang N, Wren M, Aikawa T, Holm ML, Oue H, Linares C, Allen M, Carrasquillo MM, Murray ME, Petersen RC, Ertekin-Taner N, Dickson DW, Kanekiyo T, Bu G. Alzheimers Dement. 2020.doi: 10.1002/alz.12104.

Patents: None at the time of reporting.

3. **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

Abstract: Researchers optimized methods and doses for drug regimen in animals. Since most of the experiments were being conducted in mice, having already demonstrated that blood plasma concentration increased significantly in rats after JOTROL treatment compared to non-formulated resveratrol, we confirmed that brain and blood plasma concentrations of resveratrol were increased in mice as well after JOTROL oral administration, using pharmacokinetic studies. In acute rescue studies, we determined that JOTROL had no negative effects on sensorimotor parameters in the triple transgenic Alzheimer's disease (AD) (3xTg-AD mice).

The study team observed significant increases of the non-amyloidogenic enzyme α-secretase Adam10 in the brain and decreases of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) in the liver of aged 3xTg-AD mice. It was hypothesized that JOTROL would reduce overall inflammation associated with Alzheimer's disease and help mitigate disease progression. Researchers also observed a decrease of spleen size in Alzheimer's mice orally treated with JOTROL, compared to vehicle controls. This decrease correlated with significant decreases of both TNF-alpha and IL6 expression in the spleen. This is an important observation as the long-term goal of this project would be to guide the treatment of older Alzheimer's afflicted individuals, and chronic inflammation is an intricate part of the disease. The study team also observed that JOTROL significantly increased mitochondria biogenesis in the brain of 3xTg- AD mice. This is important because decreased mitochondria function has been reported in AD. Prophylactic treatment appeared to increase cognition (or prevent cognitive decline) as determined by the novel object recognition. After prophylactic treatment with JOTROL, in the brain of 3xTg- AD mice, we also observed decreased of both tau phosphorylation at Threonine 181, decreased total tau protein levels as well as modulation of AD-related and neuroprotective genes. Pathway analyses revealed that JOTROL has a different transcriptomic profile from unformulated resveratrol, when comparing neuropathology- related genes. The study team also demonstrated that JOTROL significantly affects levels AD- related cytokines in serum, implying possible mitigation of inflammation pathways in AD pathogenesis. Researchers are still analyzing and processing data to submit a manuscript for publication this

year. The anti-inflammation aspect of JOTROL needs to be further investigated as more reports are demonstrating that microglia are one of the main culprits for neuronal cell death in AD. Researchers plan on applying for follow-on funding to the NIH to specifically investigate the effects of JOTROL on microglia-mediated effects on AD pathogenesis.

It is worth noting that recently, Jupiter Orphan Therapeutics has successfully completed a phase I clinical trial for JOTROL and there were no serious adverse events (SAEs) with significantly increased levels of resveratrol bioavailability after JOTROL administration. A phase II clinical trial is being planned.

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.

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