Alzheimer's Disease Research Grant Advisory Board

Ed and Ethel Moore Alzheimer's Disease Research Program

Fiscal Year 2022-2023 Annual Report

February 2024

Ron DeSantis
Governor

Joseph A. Ladapo, MD, PhD
State Surgeon General

2022–2023 Annual Report - Table of Contents

ED AND ETHEL MOORE ALZHEIMER'S DISEASE RESEARCH PROGRAM

INTRODUCTION AND OVERVIEW

Alzheimer's disease (AD) is the most common cause of dementia.[1] AD was officially listed as the sixth-leading cause of death in the United States in 2019 and the seventh-leading cause of death in 2020 and 2021. Between 2000 and 2019, deaths from stroke, heart disease and HIV decreased, whereas reported deaths from AD increased more than 145%.[2] AD remains the fifth-leading cause of death among Americans age 65 and older.[3]

These AD numbers are estimated to be even higher as many cases go undiagnosed. As a result, greater screening for Alzheimer's disease is needed. According to the Centers for Disease Control and Prevention, Alzheimer's disease is a progressive disease beginning with mild memory loss and possibly leading to loss of the ability to carry on a conversation and respond to the environment. Alzheimer's disease involves parts of the brain that control thought, memory, and language. It can seriously affect a person's ability to carry out daily activities. Beyond the impact of the disease on the individual, AD also affects family members who often serve as caregivers.[4] AD can span up to 20 years and is emotionally, physically, and financially challenging to caregivers.[5]

To address the impact of Alzheimer's disease in Florida, the 2014 Florida Legislature created the Ed and Ethel Moore Alzheimer's Disease Research Program (Ed and Ethel Moore Program) that was signed into law. Currently, there are 102 active ADRD research grants.

The Ed and Ethel Moore Program's long-term goals 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.

The Ed and Ethel Moore Alzheimer's Disease Research Grant Advisory Board's (Advisory Board) research agenda emphasizes the creation of intra-state research collaborations to further Florida's progress in becoming the premier state for Alzheimer's disease prevention, diagnosis, treatment, and ultimately, cure for this disease. The five research priority areas designed to address the specific needs of Floridians in relation to AD are outlined in the annual Funding Opportunity Announcement:

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.
5. Fellowships aimed at enhancing the workforce of Florida's researchers working on Alzheimer's disease.

This 2023 annual report fulfills the Advisory Board's requirement to submit a fiscal year progress report by February 15, as required by section 381.82, Florida Statutes. Legislative changes

effective July 1, 2016, require that this report also provide information regarding additional funding generated as a result of state-supported Alzheimer's research grants from this program.

ALZHEIMER'S DISEASE IMPACT AND PREVALENCE

Addressing the impact of ADRD has national importance and significance for all Americans. However, it is especially critical in Florida where the U.S. Census Bureau's latest estimates show that Florida has the highest percentage of adults aged 65 and older in the country, and this demographic remains one of the fastest growing age groups in the state.[6] Currently one out of every five Florida residents is older than 65.[7] The Alzheimer's Association projects that almost 750,000 people in Florida will have AD by the end of 2025.[8]

A study published in July of 2023, estimated the ADRD prevalence for the nation's 3,142 counties.[9] Based on their findings, the researchers estimated the highest rates of people living with AD are in Florida, Maryland, and New York.[10] Six Florida counties were included in the top 100 counties nationwide.[11] Miami-Dade County was listed first in the top ten counties nationwide (Exhibit 1).[12] The estimated number of Floridians living with AD does not include those under the age of 65, or those living with other forms of dementia, so actual prevalence may be even higher.[13] Other research also shows the impact of ADRD on families. In 2022 an estimated 827,000 Floridians provided loved ones with 1,301,000,000 combined hours of unpaid care.[14] The total value of unpaid care is now estimated to be $23,409,000,000.00.[15]

The progression of ADRD should be viewed as a continuum, over a lifetime, that researchers estimate may begin years before the brain shows the first symptoms related to memory loss.[16] 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.[17] 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.[18] Among those whose memory problems were creating functional difficulties, 42% had not shared these issues with a provider.[19]

Exhibit 1: Alzheimer's Dementia Prevalence 2023

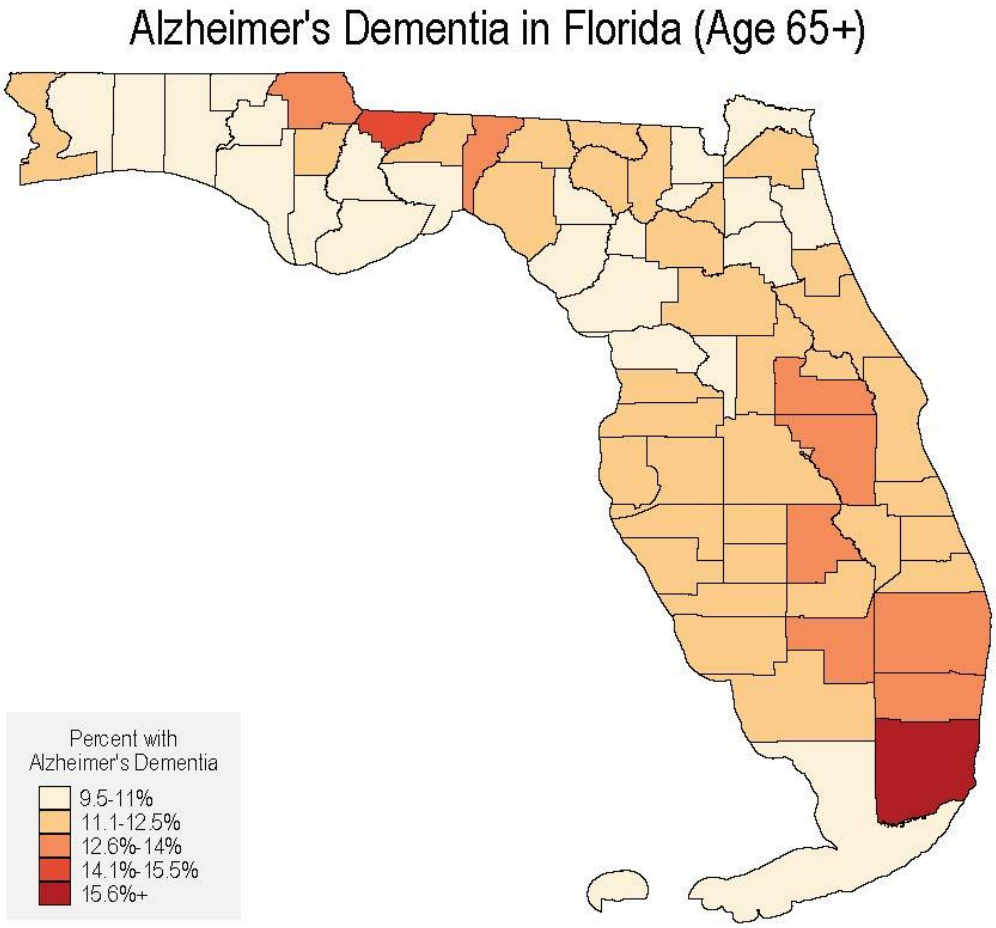


Exhibit 1: Dhana K, Beck T, Desai P, et al. (2023). Prevalence of Alzheimer's disease dementia in the 50 US states and 3142 counties: A population estimate using the 2020 bridged-race postcensal from the National Center for Health Statistics. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 19(10), 4388–4395. doi:10.1002/alz.13081.

ALZHEIMER'S DISEASE RESEARCH GRANT ADVISORY BOARD

The Advisory Board is authorized in section 381.82, Florida Statutes, and comprises 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 submits funding recommendations for proposals to the State Surgeon General by December 15 of each year. Grants and fellowships are awarded by the State Surgeon General based on scientific merit after consultation with the Advisory Board. 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 non-academic 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.[20]

Alzheimer's Disease Research Grant Advisory Board Membership

The names and positions of each Advisory Board member, as of December 15, 2023, are listed below. The second gerontologist position is currently vacant. Biographical statements or curriculum vitae are available upon request.

Gerontologists:

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

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
University of Central Florida College of Medicine

Niharika Suchak, MBBS, MHS, FACP,
Advisory Board Chair
Associate Professor, Department of Geriatrics
College of Medicine, Florida State University

Neuroscientists:

Eun-sook Yu Lee, PhD Professor
College of Pharmacy
Florida Agricultural and Mechanical University

Leonard Petrucelli, PhD
Assistant Advisory Board Chair
Chair of 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 RANKINGS FOR TOTAL NATIONAL INSTITUTE On AGING (NIA) FUNDING

Since the inception of the Ed and Ethel Moore Program in 2014, Florida has continued to increase their ADRD research infrastructure and, as a result, has also continued to receive increased federal funding that supports Florida researchers. Florida is currently positioned in the top seven for federal follow-on funding (Exhibit 2). Follow-on funding here means that researchers received federal funds due to the investment of state-level funding. According to the NIH, the total program level of funding for the federal fiscal year (FFY) 2023 was $47.7 billion.[21] Exhibit 2 shows the NIH-NIA grant funding in dollars for the top 20 states in FFY 2023:

Exhibit 2: NIH - NIA- Alzheimer's Disease Research Funding and State Rankings for FFY 2023

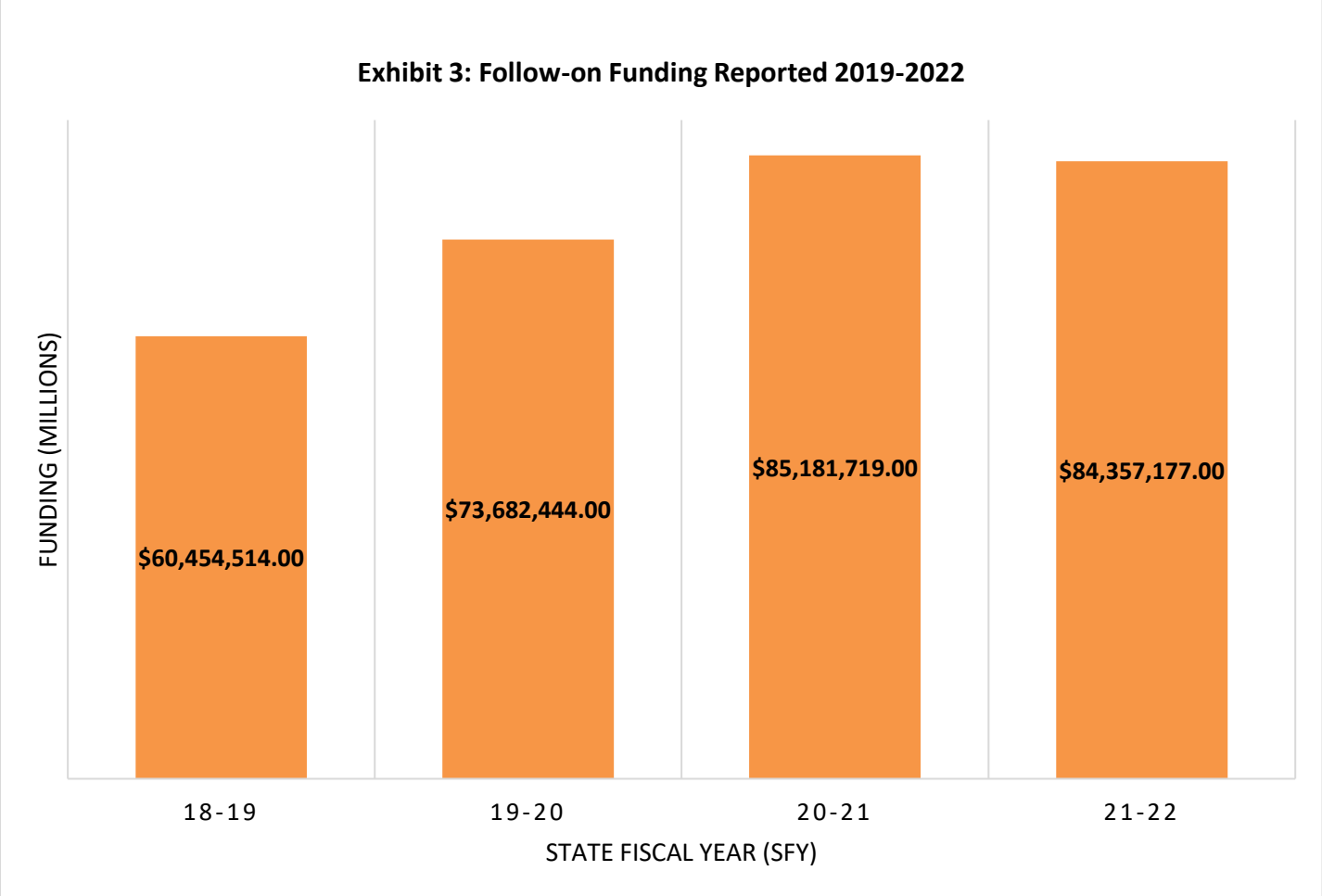
Exhibit 2: NIH Research Funding from the 2023 Fiscal Year Reporting Period: The top twenty ranked states in NIH funding are displayed. Florida is ranked seventh in the nation to receive NIA grants.

Rank	State	Number of Grants	Funding in Dollars
1	California	793	$659,742,350
2	New York	511	$375,007,101
3	Massachusetts	520	$359,505,906
4	Pennsylvania	270	$224,927,805
5	Texas	237	$179,813,474
6	North Carolina	209	$155,029,610
7	Florida	184	$153,133,650
8	Michigan	169	$133,725,827
9	Maryland	279	$125,282,907
10	Wisconsin	98	$124,381,181
11	Illinois	169	$123,696,437
12	Minnesota	140	$112,282,070
13	Missouri	102	$108,690,788
14	Washington	104	$87,164,123
15	Indiana	84	$83,327,513
16	Arizona	73	$77,986,551
17	Connecticut	95	$65,243,173
18	Georgia	97	$64,229,273
19	Ohio	118	$62,546,392
20	Rhode Island	61	$44,072,191

Source: National Center for Health Statistics, National Institutes of Health 2023. Data frozen as of 10/04/2023. Data released on 12/22/2023.[22] *NIH Awards by Location and Organization - NIH Research Portfolio Online Reporting Tools (RePORT)*

REPORTED FOLLOW-ON FUNDING FOR FLORIDA ALZHEIMER'S DISEASE RELATED RESEARCH

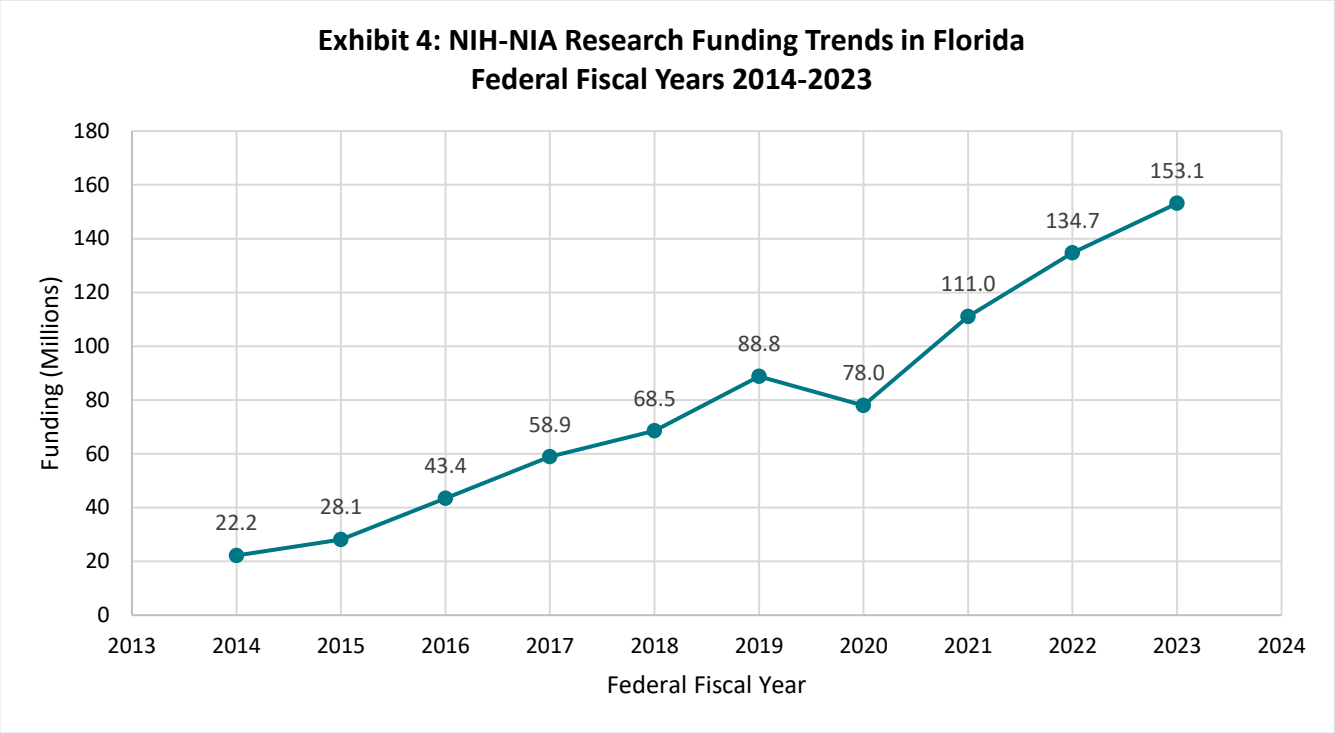
Based on self-reported data by Ed and Ethel Moore Program grant recipients, Exhibit 3 provides the follow-on funding reported by grantees based on the research funded by the Ed and Ethel Moore Program over the last four years. Follow-on funding was reported by grantees following the instruction outlined by the Legislative Progress Report forms: "List the source and amount of any federal, state, or local government grants or donations generated as a result of the research project."



Source: *Data collected from Grant Legislative Annual Reports. These are self-reported by grantees and includes all available funding sources beyond the state of Florida.*

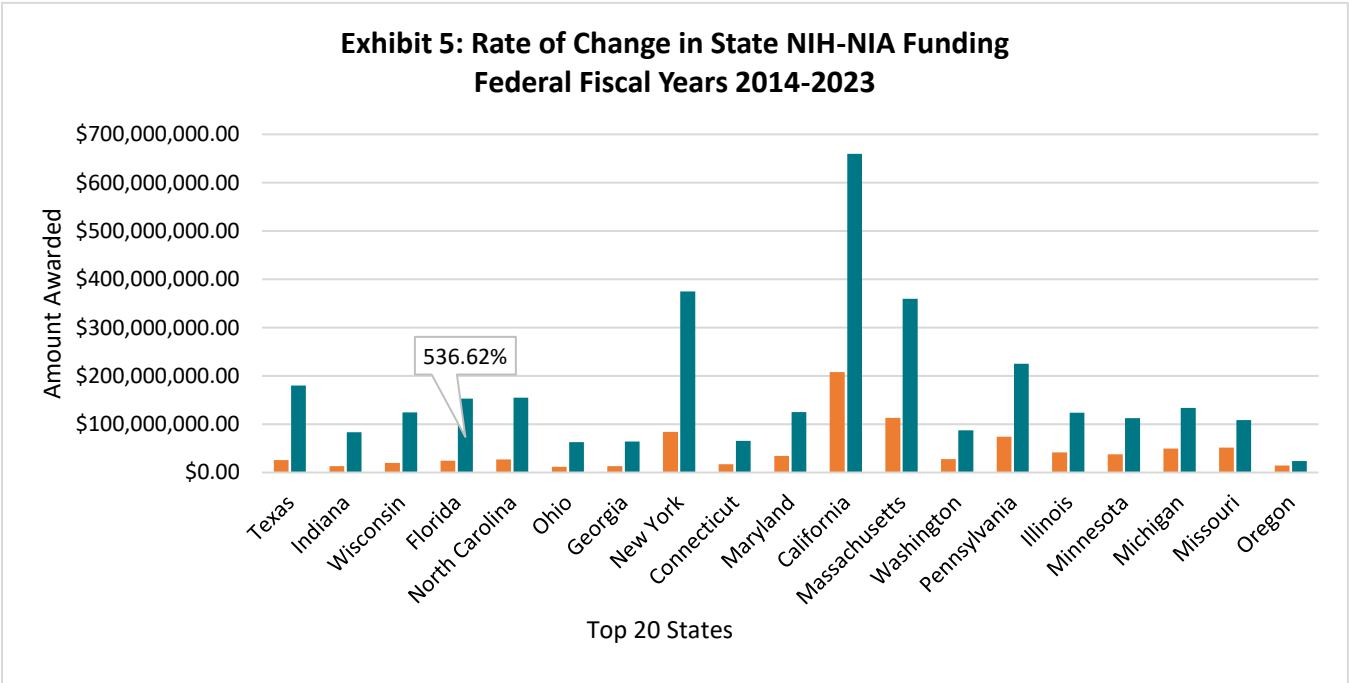
The Florida Legislature annually funds biomedical research not only for AD, but also for other grant programs managed by the Biomedical Research Section, i.e., the Live Like Bella Pediatric Cancer Research Initiative, William G. "Bill" Bankhead, Jr., and David Coley Cancer Research Program, and the James and Esther King Biomedical Research Program. As a measurement of the Florida Legislature's historic support of Florida-based research universities, hospitals and research institutions, this report also acknowledges the additional funding from the NIH and NIA received by grantees through the Ed and Ethel Moore Program as well as these other initiatives.

Exhibit 4 NIH Research Funding Trends in Florida SFY 2014-2023: This chart illustrates the growth in federal funding for Alzheimer's disease research in Florida.



Source: *National Center for Health Statistics, National Institutes of Health 2023. Data frozen as of 10/04/2023. Data released on 12/22/2023.*[23] *NIH Awards by Location and Organization - NIH Research Portfolio Online Reporting Tools (RePORT).*

Exhibit 5 Change in NIH-NIA Research Funding in the Top 20 States Fiscal Years 2014-2023: This graph displays the rate of change in federal NIH-NIA research funding for the top 20 states for fiscal years 2014-2023. Florida saw the fourth highest funding gains since 2014 (536.62%), going from $24,054,313.00 awarded in 2014 to $153,133,650.00 in 2023.



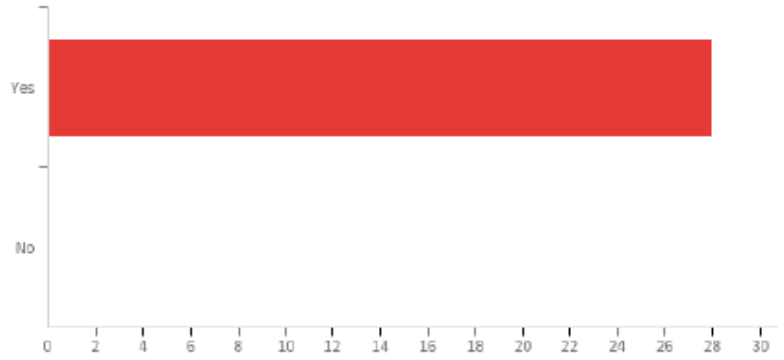
Source: *National Center for Health Statistics, National Institutes of Health 2023. Data frozen as of 10/04/2023. Data released on 12/22/2023.*[24] *NIH Awards by Location and Organization - NIH Research Portfolio Online Reporting Tools (RePORT).*

ALZHEIMER'S DISEASE RESEARCH SYMPOSIUM

The annual Ed and Ethel Moore Program hosted its disease research symposium on September 14, 2023. For the first time since its inception, two symposium tracks were available for attendees: a research track and a community track, and a total of 146 attendees registered to participate. Participants in the research track could obtain continuing education credits and a short evaluation was distributed to those who registered. See Exhibit 6 for a summary of responses following the symposium.

Exhibit 6: Evaluation Summary Ed and Ethel Moore Alzheimer's Disease Research Symposium 9/14/23. Administered by Suwannee River Area Health Education Center (AHEC)**.**

This program offered knowledge and/or skills that will help me provide better patient/client care.



#	Field	Minimum	Maximum	Mean	Std Deviation	Variance	Count
1	This program offered knowledge and/or skills that will help me provide better patient/client care.	1.00	1.00	1.00	0.00	0.00	28

#	Answer	%	Count
1	Yes	100.00%	28
2	No	0.00%	0
	Total	100%	28

Respondents were asked to share feedback regarding their experience at the symposium. Of note, the Biomedical Research Section received written comments from participants about the value provided by the community track which focused on the impact of research, available resources, and health outcomes. This feedback demonstrates not only the success of the symposium but also meets the goals of the Ed and Ethel Moore Program in fostering collaboration amongst researchers in the state.

PROGRESS TOWARD PROGRAMMATIC GOALS

In SFY 2023-24, the Legislature provided $5 million for research grants. Appendix A details all newly awarded grants and Appendix B details previously awarded active grants. Appendix B provides information on research progress, follow-on funding, publications, and patents for each previously awarded active grant. Appendix C provides information on research grants that closed within the past state fiscal year.

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

During SFY 2023-24, 19 grantees received research funding. Without this funding, many important scientific advancements and discoveries in Alzheimer's disease would not be possible. As discussed earlier in this report, there is a growing need to address the concerns of ADRD in Florida. In response to this growing need, the Advisory Board recommends options to expand the reach of the Ed and Ethel Moore program in the following areas:

1. **Increasing research funding:** Since 2015, funding for the Ed and Ethel Moore Program has remained constant. Approximately 30% of all applicants receive Ed and Ethel Moore Program grant funding. Standard and pilot grants are most frequently funded. Additional funding would allow funding for consortium grants that could provide for increased collaboration on how to best combat Alzheimer's disease.[25]

2. **Establishing a registry:** Economics research estimates that over a ten-year period, a statewide dementia registry could slow the growth in health care spending and estimates a ten dollar return on every dollar invested.[26] The economic return is complemented by non-tangible benefits such as: improved access to evidence-based best practice, collaboration, and assistance with implementing effective public health interventions.[27]

3. **Increasing provider education:** In 2021 there were 362 geriatricians in Florida. Estimates are that a 277% increase in geriatricians will be needed to meet the demand by 2050.[28] The Ramping up Education of Alzheimer's Disease and Dementia for You (READY) Act focuses on educating current providers on ADRD issues and resources. The lack of dedicated funding for Project READY limits the Biomedical Research Section's ability to support and expand the program. Increasing funding for Project READY would provide the opportunity for advancing AD education through sharing state-funded AD research, determining a baseline of existing data, and in establishing Florida as a national leader in ADRD care.

RAMPING UP EDUCATION OF ALZHEIMER'S DISEASE AND DEMENTIA FOR YOU ACT

The READY Act promotes guidance and education to help health care providers improve care and services for their patients with Alzheimer's disease and dementias. Timely interventions can mean a higher quality of life for many Floridians. The READY Act recommends that health care providers:

- Use validated cognitive assessment tools to screen patients aged 65 and older during yearly Medicare wellness visits. The Florida Department of Health (DOH) suggests using assessment tools and the guidelines index from the Alzheimer's Association.

- Practice early detection and timely diagnoses. Just as screening for health conditions and diseases like diabetes, heart disease, and cancer gives people access to preventive health services and early diagnosis, the same is true for Alzheimer's disease and dementias. Cognitive decline can be difficult and time-consuming to discuss with patients, but there are many assessment tools for limited-time office visits provided by the Alzheimer's Association.

- Use Medicare CPT code 99483 for a clinical visit that leads to a comprehensive care plan. Care planning is beneficial because it gives patients and caregivers opportunities to learn about medical and non-medical treatments, clinical trials, and services available in the community. Physicians, physician assistants, nurse practitioners, clinical nurse specialists and certified nurse midwives can be reimbursed. Because care planning for people with dementia is an ongoing process, care plans should be updated at least once a year or when disease has progressed.

- DOH recommends the Alzheimer's Association's Cognitive Impairment Care Planning Toolkit.

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

Appendix A: Newly Awarded Active Grant Details
Funded Fiscal Year 2023-2024

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
24A01	Florida Atlantic University	Ruth Tappen, EdD, RN, FAAN	$350,000.00	2/28/2027	No	No	No
24A02	Florida Atlantic University	Mare Cudic, PhD	$350,000.00	2/28/2027	No	No	No
24A03	Florida Atlantic University	Qi Zhang, PhD	$350,000.00	2/28/2028	No	No	No
24A04	Florida State University	Choogon Lee, PhD	$350,000.00	2/28/2027	No	No	No
24A05	Florida State University	Ravinder Nagpal, PhD	$100,000.00	2/28/2026	No	No	No
24A06	Mayo Clinic Florida	Wenhui Qiao, PhD	$100,000.00	2/28/2026	No	No	No
24A07	Mayo Clinic Florida	Yonghe Li, PhD	$350,000.00	2/28/2027	No	No	No
24A08	Mayo Clinic Florida	Daisuke Ono, MD, PhD	$100,000.00	2/28/2026	No	No	No
24A09	Mayo Clinic Florida	Minerva Carrasquillo, PhD	$350,000.00	2/28/2026	No	No	No
24A10	Mayo Clinic Florida	Pamela McLean, PhD	$100,000.00	2/28/2025	No	No	No
24A11	Nova Southeastern University	Mary Holschbach, PhD	$100,000.00	2/28/2025	No	No	No
24A12	University of Central Florida	Michal Masternak, PhD	$349,999.00	2/28/2028	No	No	No
24A13	University of Florida	Jeremy Grant, PhD	$95,556.00	2/28/2026	No	No	No
24A14	University of Florida	Abbas Babajani-Feremi, PhD	$349,749.00	2/28/2028	No	No	No
24A15	University of Florida	Carla Fisher, PhD	$99,991.00	2/28/2026	No	No	No
24A16	University of Miami Miller School of Medicine	Philip Harvey, PhD	$99,999.00	2/28/2026	No	No	No
24A17	University of Miami Miller School of Medicine	Rosie Curiel Cid, PsyD	$99,987.00	2/28/2025	No	No	No
24A18	University of Miami	Holly Cukier, PhD	$350,000.00	2/28/2027	No	No	No
24A20	Mayo Clinic Florida	Thomas Caulfield, PhD	$165,241.00	2/28/2027	No	No	No

1. **Grant #:** 24A01

Principal Investigator: Ruth Tappen, EdD, RN, FAAN

Organization: Florida Atlantic University

Summary: The purpose of this study is to develop and test a rapid, easily administered screening test of older drivers who are experiencing cognitive decline called Fit2Drive Online. Fit2Drive Online provides an objective, evidence-based prediction of the older driver's ability to pass an on-road driver evaluation, which is the "gold standard" of older driver evaluation. It is well-documented that most individuals with mild cognitive impairment (MCI) or the earliest stages of Alzheimer's disease or related dementia (AD/ADRD) remain able to drive safely. As the disease progresses, however, the individual loses this ability. The point at which this occurs is very difficult for the individual to recognize, families to assess, or clinicians to determine in an office setting. Discussion of driving cessation provokes passion, frustration, and fear in individuals experiencing cognitive decline, reported by their family caregivers as one of the most difficult decisions families had to make. Likewise, healthcare providers, especially primary care providers, report feeling unprepared to provide definitive guidance on the subject. The research

team anticipates that results obtained from Fit2Drive Online would be welcomed by members of all three groups.To accomplish this goal, researchers will first upload the cognitive tests that were the best predictors in the preliminary Fit2Drive research along with carefully selected additional tests that have evidenced predictive power related to driving ability onto tablets, then test them on a sample of 150 participants who exhibit a wide range of impairment from normal, unimpaired older adults recruited from the community to clients of the Memory Center ranging from pre-MCI to moderately impaired (beyond that level individuals are unable to drive safely and cannot be taken on the road for a driving test). Analysis of the results will be directed toward identifying the tests with the greatest power to predict on-road driving performance requiring the smallest number of items and/or shortest testing time. The selected tests, comprising Fit2Drive Online, along with the algorithm for predicting ability to pass the on-road test, will be uploaded onto the tablets and tested on an additional 200 participants. Providers and/or their trained staff will conduct this second phase of testing in clinical settings. Participants, family caregivers, and providers will be asked to rate the acceptability, ease of administration, and effectiveness in achieving patient agreement to either driving cessation or to follow-up evaluation when these results are indicated. The results of this study will provide a strong foundation for seeking funding from National Institute on Aging (NIA) to conduct a randomized controlled trial (RCT) of the effectiveness of this novel screening tool in clinical settings.

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 #:** 24A02

Principal Investigator: Mare Cudic, PhD

Organization: Florida Atlantic University

Summary: Neuronal disorders, such as Alzheimer's disease (AD), are among the most pressing problems for aging populations in the world. The staggering costs of long-term management of AD patients require new preventive, diagnostic, and therapeutic approaches. AD is characterized by the accumulation of the neurotoxic deposits of amyloid beta peptide (Aβ) within the brain along with the neurofibrillary tangles, aggregates of hyperphosphorylated tau protein. Recent evidence indicates that microglial activation is critical for the pathogenesis of AD, however, the role of microglia in the amyloid-associated neuron loss is not well understood. Knowing the importance of protein glycosylation in mediating a plethora of biological functions, and because most known AD-related molecules are either modified with glycans or play a role in glycan regulation, glycobiology represent an interesting new insight into the understanding of AD, and a potential for new therapeutic approaches. Recently research staff have demonstrated the unique role of O-glycosylation on amyloid precursor protein's (APP's) secondary structure, proteolytic cleavage by beta (β)- and alpha (α)-secretase, aggregation properties and provided an important insight into glycosylation-driven changes of the intrinsic properties of APP-derived

glycopeptide models. Considering well-documented support for the relevance of glycosylation in inflammation and innate immune responses, the researchers hypothesize that APP O-glycosylation in the proximity of secretase cleavage sites may result in imbalance between production and clearance of Aβ peptides and affect the microglia activation. To test this hypothesis, researchers propose to take advantage of the synthetic chemistry strategies developed in the group, to prepare APP glycopeptide models found within short peptide fragments from cerebrospinal fluid of AD patients, evaluate their stability towards proteolytic enzymes, and the type of inflammatory microglia response upon glycopeptide stimulus. These studies will shed light into a rather unexplored area in AD and open avenues for development of novel therapeutic strategies to curb the frightening surge of AD and other neurodegenerative diseases.

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 #:** 24A03

Principal Investigator: Qi Zhang, PhD

Organization: Florida Atlantic University

Summary: Ever since Dr. Alzheimer's 1906 report, research on Alzheimer's disease (AD) has been focused on proteins and genes pathologically or genetically linked to AD. However, more and more new evidence has revealed significant abnormalities in brain lipids, especially cholesterol (Chol). Chol is highly enriched in the brain (possessing around 20% total body Chol) and extremely crucial for neuronal function and survival. Particularly, Chol is indispensable for synaptic vesicles (SVs), neurotransmission, and axon integrity. Generally, astrocytes produce Chol and supply it to neurons by lipoprotein like apolipoprotein E (ApoE). Interestingly, ApoE4, one of the three ApoE isoforms (i.e., ApoE2, 3, and 4), is the greatest genetic risk factor for the most common type of AD, sporadic AD. Reportedly, ApoE4 is less capable of transporting Chol. On the other hand, the human brain experiences a progressive decrease during aging. And aging is the primary risk factor more prominent than any other genetic or environmental factors. The latest papers show that amyloid precursor protein (APP) regulates axonal Chol and that amyloid precursor protein (APP) deletion or mutations cause Chol deficiency in mouse and human neurons. More intriguingly, aging APP-null mice exhibit Chol abnormality, Tau hyperphosphorylation, axon breakdown, and gliosis, all of which have been found in the brain of AD patients. Therefore, researchers hypothesize that different AD risk factors converge on brain Chol whose dysregulation triggers synaptic dysfunction and neurodegeneration. To test the hypothesis, the researchers propose three specific aims. First, research staff will combine ribonucleic acid (RNA) sequencing and mass spectrometry to identify transcriptomic and lipidomic changes in the aging mouse brain. Second, research staff will use adult mouse brain slices and induced pluripotent stem cell (iPSC)-derived human neurons to test if Chol deficiency

triggers neuronal loss. Third, research staff will test if and how brain-permeable statins or adenosine triphosphate-binding cassette transporter (ABCA1) agonists affect synaptic transmission and neuronal survival by increasing or decreasing Chol respectively. To pursue these specific aims, research staff will develop novel imaging tools for brain Chol, employ genome editing in human iPSCs, and harness the power of multi-omics. All of those methodologies have been successfully adopted in this ongoing research and reported in recent publications. This project, if successful, will provide much-needed insight into brain Chol, AD pathogenesis, and potential therapeutic strategy.

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 #:** 24A04

Principal Investigator: Choogon Lee, PhD

Organization: Florida State University

Summary: Alzheimer's disease (AD) is a devastating proteinopathy affecting millions, without effective treatments. Although AD is best known for cognitive impairment and dementia, sleep disorders have long been recognized as both a comorbidity and a potential causative factor in AD. The bidirectional effects between AD and sleep disorders are believed to produce a vicious positive feedback loop in AD pathogenesis. Current insomnia drugs such as gamma-aminobutyric acid (GABA)ergics may improve sleep but could increase the risk of serious falls due to hangover effects. Thus, there is a critical need to develop better therapies that interrupt the vicious cycle to slow or stop disease progression and improve the quality of life for patients and caregivers.Recent data from multiple groups including this one have linked sleep disorders in AD to deficits in total sleep time and in the amplitude of circadian rhythms and the efficiency of the glymphatic system for waste clearance in the brain. There is a component of AD sleep disturbance due to irreversible tissue damage/neuronal loss, but the deficits the research staff are studying should be treatable with the right mechanistic insights. This research team and others have shown that sleep time is reduced, and the circadian sleep cycle is unstable and fragmented in AD patients potentially because the circadian clock's amplitude is dampened, lowering the thresholds between wake and sleep and diminishing the depth of sleep. The research team have thus hypothesized that treatments that enhance circadian rhythms amplitude could ameliorate sleep disorders and increase sleep duration in AD. Restoring healthy circadian rhythms and sleep should also improve the waste clearance system of brain, the glymphatic system, which is under control of the circadian clock. Researchers thus hypothesize that the right intervention could simultaneously restore healthy sleep cycles and promote efficient elimination of toxic proteins and proinflammatory metabolites, thus delaying or stopping disease progression and reduce vascular inflammation.The orexin pathway has been established as an important regulator of wake/sleep cycles, and drugs antagonizing this

pathway (e.g., suvorexant) are effective for treating primary and secondary insomnias, with fewer adverse effects compared to other sleep drugs. Moreover, prior work suggests that orexin signaling may regulate circadian clock function. To begin, the research team will administer suvorexant into transgenic mice emulating early stages of AD and measure their wake/sleep cycles and glymphatic function (using MRI and other measures). The preliminary data showed that the orexin antagonist improved sleep quality in these mice. Then the research team will administer suvorexant into a novel circadian mutant mouse model emulating severe sleep fragmentation (similar to later stages of AD) and measure efficacy of the drug on sleep quality and glymphatic function. Because the only defect in the mouse model is reduced circadian amplitude, results from this study will provide direct mechanistic insights into how orexin antagonists affect the circadian clock, not only in AD but also in the context of other insomnias.If successful, this research would support clinical studies of orexin antagonists and novel combination drugs for AD patients, not only to treat sleep disorders but also to potentially slow disease progression.

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 #:** 24A05

Principal Investigator: Ravinder Nagpal, PhD

Organization: Florida State University

Summary: Despite decades of research, the etiology of Alzheimer's disease (AD) remains unresolved, underscoring the need to address this devastating disorder from a different perspective. Pathologically produced amyloid beta (Aβ) and tau proteins have long been believed to be the cause of AD, but the failure of clinical studies targeting amyloid and tau cascades underscores the need to explore novel hypotheses that can explain AD etiology and help discovering novel therapies for prevention and cure of AD. Researchers have recently discovered that the at-risk AD patients with cognitive impairment harbor an abnormal gut microbiome, with specific pathogens associated with the cerebrospinal amyloid and tau levels, underscoring the role of the gut-microbiome-brain axis in AD. Specifically, the research team noted abnormally higher levels of Klebsiella pneumoniae (Kpn), an opportunistic pathogen classified as emerging public health concern due to antibiotic-resistance acquisition, in these patients. Kpn infections are mostly hospital-acquired and occur mostly in elderly subjects. Several Kpn strains and outbreaks have been reported in the United States. including Florida, and several studies have reported higher Kpn infections in patients with dementia and impaired cognition, but the causative role of Kpn infection in AD remains unknown. Establishing a preclinical mouse model of Kpn infection, the researchers have revealed that the Kpn, particularly following the antibiotic therapy, can translocate from gut to blood via breaching the gut epithelial barrier. Evidently, once present in the circulation, Kpn is also able to infect brain

via blood-brain barrier to trigger neuroinflammation and neurocognitive dysfunction. Several National Institute of Health (NIH) studies have reported the presence of infectious microbes in the brain of AD patients, suggesting a link between microbial pathogens and the emergence of the antimicrobial protection hypothesis of AD and that AD triggers could be of infectious/innate immune origin, particularly because AD develops decades before clinical symptoms appear. These studies evidently link Kpn infection with AD, but the role of Kpn pathogenesis in AD neuro-etiology remains unknown. To address this gap in knowledge, this proposal aims to integrate a model of Kpn pathogenesis with that of AD neuropathogenesis to determine the mechanisms via which the Kpn enteric infection triggers and/or aggravates AD-related neuroinflammation and neurocognitive impairment via the gut-blood-brain axis. The overarching hypothesis is that the Kpn enteric infection, in concurrence with antibiotic-induced gut dysbiosis, instigates the translocation of Kpn from gut to blood and then to brain via crossing the impaired gut-blood-brain barrier, thereby triggering/ aggravating neuroinflammation and amyloid-beta and tau pathology leading to AD-associated neurodegeneration and neurocognitive impairment. This will be the first known study integrating a preclinical model of AD with that of antibiotic-induced Kpn pathobiome and gut dysbiosis to investigate whether and how this gut pathobiome impairs gut-blood-brain axis and impacts AD-associated neuroinflammation and neurocognitive functioning. These pioneering studies are poised to disentangle the putative role of infectious agents in AD neuropathology and will advance efforts focused on preventing and managing AD via microbiological, nutritional and/or pharmacological (e.g., probiotics, prebiotics, postbiotics, microbial transplants, immune-therapeutics) interventions.

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 #:** 24A06

Principal Investigator: Wenhui Qiao, PhD

Organization: Mayo Clinic Florida

Summary: The apolipoprotein E (APOE) gene is the strongest genetic risk factor for Alzheimer's disease (AD), with the APOE4 allele increasing the risk while APOE2 has a protective effect compared to APOE3. Approximately 26% of the population carries the APOE4 allele, and individuals with this allele experience accelerated memory decline and impaired clearance of toxic amyloid beta (Aβ), leading to the accumulation of Aβ and subsequent brain dysfunction. However, the exact mechanisms by which APOE4 contributes to AD progression and potential therapeutic interventions are still not fully understood. The APOE protein plays a vital role in cholesterol transportation and lipid balance in various cell types within the brain. Oligodendrocytes (OLs), derived from oligodendrocyte precursor cells (OPCs), are responsible for forming myelin around neuronal axons, which ensures stable brain activity and information processing. Maintaining proper APOE-regulated lipid homeostasis is crucial for OPC and OL

function. However, recent studies have revealed that APOE4 compromises OL function by disrupting lipid regulation and causing lipid accumulation, thereby exacerbating AD pathogenesis. Based on the well-documented detrimental effects (gain-of-toxic function) associated with APOE4 in cellular and brain functions, the researchers hypothesize that removing APOE4 specifically from OPCs can modify the lipid profile and improve OPC and OL functions, thus affecting myelin status, neuronal function, cognition, and AD pathogenesis. To test this hypothesis, researcgers have generated mouse models of platelet-derived growth factor receptor alpha (Pdgfra) Cre recombinase (CreER)/+; APOE3flox/flox and PdgfraCreER/+; APOE4flox/flox. Researchers can induce APOE deletion in OPCs (referred to as APOE-oKO) at 1.5 months of age by administering tamoxifen treatment, while using corn oil-treated mice as controls (without APOE deletion). This research will focus on two specific aims. Research staff will investigate the effects of OPC-APOE3 or OPC-APOE4 deletion on cognitive, neuronal, OPC, and OL functions. These assessments will include evaluating memory performance, synaptic plasticity and integrity, OPC proliferation and differentiation, and myelination status in APOE-oKO mice at six months of age. Research staff will then cross the APOE-oKO mice with the 5xFAD amyloid mouse model to examine the impact of OPC-APOE deletion on amyloid pathogenesis. The research team will evaluate Aβ deposition, glial response, myelination status, and lipid homeostasis in 5xFAD/APOE-oKO mice at ten months of age. Researchers will also analyze the synaptic integrity and neuritic dystrophy to evaluate the Aβ related neuronal toxicity. All of these assessments will allow researchers to test the therapeutic potential of removing OPC-APOE4 to reduce amyloid pathologies. Additionally, the researchers will conduct single-nuclei ribonucleic acid (RNA) sequencing to understand the molecular signature of OPCs, OLs, and other cell types at the single cell level. In summary, the proposed therapeutic strategy aims to examine the effects of OPC-APOE deletion on brain functions and the development of AD. The successful completion of these studies will provide a fundamental foundation for APOE4-targeted AD therapy and offer comprehensive and unique insights into the roles of OPCs and OPC-APOE in brain function and AD pathologies.

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 #:** 24A07

Principal Investigator: Yonghe Li, PhD

Organization: Mayo Clinic Florida

Summary: Alzheimer's disease (AD) is the most common form of age-related neurodegenerative disease characterized by detrimental cognitive impairments with the pathological amyloid-beta (Aβ) plaques and tau-containing neurofibrillary tangles (NFTs) as the two major hallmarks of this incurable disease. The current AD therapies are dominated by symptomatic treatments with three inhibitors of cholinesterase and one blocker of N-methyl-D-

aspartate (NMDA) receptor, which partially ameliorate cognitive and behavioral symptoms in AD patients for a short period. Aducanmab and Lecanemab are two potential disease-modifying therapies approved by the Food and Drug Administration (FDA) in the past two years, but their clinical benefits need further investigation. Thus, there is an urgent need to develop new therapeutic strategies for AD treatment. Histone deacetylases (HDACs) play critical roles in the epigenetic regulation of gene expression and are associated with synaptic plasticity and cognitive function in the brain. Studies have demonstrated that class I HDACs (HDAC1, 2, 3 and 8) negatively regulate memory formation and synaptic plasticity, and that inhibition of class 1 HDACs reverses memory deficits in mouse AD models. Therefore, inhibition of class I HDACs is a promising therapeutic strategy for AD therapy. Wnt/β-catenin signaling is not only crucial for neuronal survival and neurogenesis, but also plays important roles in regulating synaptic plasticity and blood-brain barrier (BBB) integrity and function. Mounting evidence indicates that Wnt/β-catenin signaling is diminished by multiple pathogenic pathways in AD brain. Particularly, two single-nucleotide polymorphism (SNPs) and an alternative splice variant of Wnt co-receptor lipoprotein receptor-related protein 6 (LRP6) display impaired the signaling activity and accelerate synapse degeneration during aging and in AD, and consequently increase the risk of developing AD. Therefore, restoring Wnt/β-catenin signaling is an attractive strategy for AD therapy. In the preliminary studies, the research staff have discovered a series of novel biofunctional small molecules which activate Wnt/β-catenin signaling and inhibit class I HDAC activity. The leading compound W2A-68 displays great potency in activation of Wnt/β-catenin signaling (EC50 = 298 ± 25 nM) and inhibition of HDAC1, 2 and 3 activities (IC50 values of 35 nM, 94 nM and 49 nM, respectively). In addition, W2A-68 has no or weak activity against other HDACs. Critically, W2A-68 has excellent aqueous solubility and microsomal stability and is able to penetrate well into the brain. Moreover, W2A-68 inhibits tau phosphorylation in patient-specific induced pluripotent stem cell (iPSC)-derived cerebral organoids. The research team herein proposed a collaborative effort to study the therapeutic effects of W2A-68 in patient-specific iPSC-derived in vitro models and determine preventive/therapeutic effects of W2A-68 in AD mouse models. Successful completion of current study will allow researchers to develop a novel candidate for the treatment of 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 #:** 24A08

Principal Investigator: Daisuke Ono, MD, PhD

Organization: Mayo Clinic Florida

Summary: Background: Alzheimer's disease (AD) is typically characterized by memory loss and other cognitive impairments. Motor symptoms, particularly parkinsonism, in AD patients are often attributed to other comorbid neuropathologies such as Lewy body disease (LBD). A

postmortem study, however, reported that 22% of AD patients exhibited parkinsonism, with 43% of them lacking other neuropathologies. Furthermore, 83% of the AD patients showed various degrees of neuronal loss in the substantia nigra (SN), a region associated with parkinsonism. Previous studies assessing neuronal loss in the SN have relied on manual counting or semi-quantitative scoring, which potentially have limitations, such as inter-rater variability, sampling bias, and lack of scalability. Thus, the significance of nigral pathology in AD remains poorly understood due to methodological constraints. To address these issues, the research team developed a machine learning (ML)-based software that automatically counts neurons within the SN from a whole slide image (WSI) of the midbrain section stained with hematoxylin and eosin (H&E). Research staff finetuned YOLOv8 pre-trained models for two different tasks, with manual annotations as a reference: segmentation of the SN and detection of nigral neurons. The software successfully counted nigral neurons in 104 AD cases without other major neurodegenerative diseases from the Mayo Clinic brain bank. In the pilot study, 19 AD cases with nigral neuronal loss and 20 AD cases without nigral neuronal loss were selected for immunohistochemistry (IHC) of transactive responsedeoxyribonucleic acid-binging protein (TDP-43), tau, and α-synuclein in the SN. Among the cases with nigral neuronal loss, 26% presented TDP-43 pathology, while none of the cases without neuronal loss had this pathology. Tau was positive in all 39 cases, whereas comorbid Lewy bodies were observed in one case with nigral neuronal loss. The preliminary findings suggest that some AD cases with nigral neurodegeneration might not be associated with concurrent LBD, but possibly with tau or TDP-43 pathology. Based on the results, the researchers propose a data-driven approach to characterizing the clinicopathologic link between parkinsonism and nigral pathology in AD without other neurodegenerative diseases. The research team will aim to develop an automated pipeline to quantify neuronal populations in the SN and assess neuropathologic burdens of tau and TDP-43. ML models for segmenting positive regions in IHC for tau and TDP-43 will be fine-tuned using manual annotations as a reference and integrated into the existing pipeline. By applying the pipeline to 200 cases, research staff will obtain nigral neuron counts from hematoxylin and eosin stain (H&E) stained slides, as well as measure the burdens of tau and TDP-43 from corresponding IHC slides. Then the researchers will explore the clinicopathologic correlation between nigral pathology and parkinsonism. Clinical information will be extracted from medical records using a dedicated Python program, ensuring objectivity and scalability. Researchers will then investigate the neuropathologic contributing factors for parkinsonism using data-driven ML algorithms, in addition to conventional statistical approaches. This study aims to elucidate the clinicopathologic link between parkinsonism and nigral pathology in AD. Given the current implementation of disease-specific treatments for neurodegenerative diseases, understanding the underlying pathology of parkinsonism in AD has significant implications for precise diagnosis and therapeutic strategies for patients 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.

9. **Grant #:** 24A09

Principal Investigator: Minerva Carrasquillo, PhD

Organization: Mayo Clinic Florida

Summary: With the recent Food and Drug Administration (FDA) approval of two therapies for Alzheimer's disease (AD) that appear to improve cognitive symptoms in some patients by directly targeting the disease pathology, the promise of effective AD therapies is becoming a reality. Now more than ever the ability to accurately diagnose AD and follow the disease progression is essential to ensure that novel treatments are prescribed to patients that are most likely to benefit from them. However, diagnosing AD remains challenging due to symptom heterogeneity. To accurately diagnose AD, the presence of amyloid beta (Aß) plaques and neurofibrillary tau tangles must be demonstrated, which until recently could only be achieved with neuroimaging or cerebrospinal fluid biomarkers of Aß and tau. The development of sensitive plasma Aß and tau assays may enhance accessibility to accurate diagnosis through their less invasive nature and reduced cost. Yet, evaluation of these plasma assays has not been performed across all populations. Underrepresented groups such as African Americans (AA), would benefit from increased inclusion in such studies given that their risk of developing AD is twice that of non-Hispanic whites (NHW). This research group has begun to tackle this health disparity, analyzing plasma samples from AA AD cases and controls as part of the Florida Consortium for African American Alzheimer's Disease Studies (FCA3DS) led by this group. In an article published in 2021, this research group reported the evaluation in plasma of five markers of AD pathology and neuroinflammation in 321 FCA3DS participants. Of the five plasma proteins tested (Aß42, total tau, IL6, IL10 and TNFα), total tau showed a significant association with higher levels in the AD group. Yet, the predictive value of total tau was not sufficient to fully discriminate AD cases versus controls. Recent studies in NHW cohorts have shown that detection of specific phosphorylated tau residues, such as p-tau217, in plasma can discriminate AD versus controls more effectively than total tau, and that the combined analysis of plasma Aß42/Aß40 ratio with glial fibrillary acidic protein (GFAP) and APOE-ε4 status, or p-tau217 combined with APOE-ε4 status and cognitive tests yielded the greatest predictive value of AD diagnosis. Therefore, in this application, the research staff propose to test these plasma markers of AD neuropathology, neuroinflammation and neurodegeneration in the FCA3DS cohort to determine the optimal plasma biomarker combination for AD prediction in AA. The specific aims of this project are to: measure the concentration of ptau217, Aß42, Aß40, and ptau217, GFAP and neurofilament light (NfL) in existing plasma from >500 FCA3DS participants; test the relationship of these plasma measures individually with AD diagnosis; determine the optimal combination for an accurate diagnosis of AD using ptau217, Aß42, Aß40, and ptau217, GFAP and NfL and >7,000 other proteins detected in plasma already being measured in this cohort. Thus, the proposed work will address the need for improved AD diagnosis in AA, an understudied and underserved population at greater risk of developing AD, by enabling the development of less invasive, and more accessible, biomarkers of AD. This proposal addresses Priority Area 4 of the 2023 Ed and Ethel Moore Alzheimer's Disease Research Program, as the proposed studies focus on improved AD diagnosis in AA, an

understudied population (Focus Area 4.1.), and developing less invasive, early biomarkers (Focus Area 4.3).

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 #:** 24A10

Principal Investigator: Pamela McLean, PhD

Organization: Mayo Clinic Florida

Summary: The goal of this project is to advance the mechanistic understanding of the role that alpha-synuclein plays in disease pathogenesis and progression of Alzheimer disease related dementias (ADRDs) such as Lewy body dementia (LBD) by discovering molecular interactors of alpha-synuclein and defining the αsyn aggregate interactome (aggretome). Herein the research staff propose a pilot project that will serve to generate preliminary data for a future investigator-initiated award to Naitonal Institute of Health (NIH). Researchers hypothesize that the molecular environment of alpha-synuclein contributes to ADRD disease processes, and that proximity proteomics can be applied to capture the molecular microenvironment surrounding alpha-synuclein and reveal key players in the aggregation process. Proximity-dependent biotin identification (BioID) technology fuses a promiscuous biotin ligase enzyme—a mutant form of the escherichia coli biotin ligase enzyme BirA (R118G) (referred to as BirA*)—to a protein of interest (the bait, in this case alpha-synuclein) in living cells thus enabling biotinylation of proximal interacting proteins (<100Å or <10 nm). Proximal biotinylated proteins can then be isolated via affinity purification and identified by mass spectrometry. Here researchers have developed a novel split-BirA* alpha-synuclein system to differentiate molecular interactors of αsyn monomers, oligomers, and aggregates and define the alpha-synuclein interactome or aggretome. In split-BirA* the inactive N-terminal 98 amino acids of BirA* is fused to the N-terminus of αsyn (NBirA*-αsyn), and the inactive C-terminal 223 amino acids of BirA* is fused to the C-terminus of αsyn (αsyn-CBirA*) such that αsyn-αsyn interactions reconstitute the active BirA* enzyme and result in promiscuous biotinylation of proteins close to αsyn. Herein, the researchers propose to test the hypothesis that the alpha-synuclein aggretome contains proteins that are unique from proteins interacting with alpha-synuclein monomers and play a role in the aggregation processes in three specific aims. The researchers will capture and identify proteins in proximity to alpha-synuclein monomers and oligomers in stable cell lines. Researchers will then identify proteins in proximity to phosphorylated alpha-synuclein aggregates induced by the addition of proteopathic seeds. Finally, the researchers will validate a role for alpha-synuclein aggretome-associated proteins in neurodegenerative processes in human post-mortem brain specimens from the Mayo Clinic brain bank. Successful completion of this project will nominate novel molecular interactors and cellular pathways regulating the aggregation of alpha-synuclein and contributing to the pathogenesis of LBD and ADRDs and will

lead to future mechanistic and functional studies to identify potential new therapeutic targets for effective treatments of LBD.

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 #:** 24A16

Principal Investigator: Philip Harvey, PhD

Organization: University of Miami Miller School of Medicine

Summary: Promoting cognitive health and functional independence among the vast growing older adult population is a key national priority. Promising data has emerged about the effectiveness of targeted cognitive training interventions to improve the cognitive skills and functional outcomes of older adults, which are essential to independent living. This 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 these researchers bring to 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 postdoctoral 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 the 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 the expertise in cognition, aging, functional skills training and the neurosciences. Dr. Rosie Curiel Cid, and David Loewenstein, core CNSA faculty members, would serve as secondary mentors. Each mentor offers unique but complementary experience. The University of Miami Brain Health Pavilion and the large National Institutes of Health (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.

12. **Grant #:** 24A12

Principal Investigator: Michal Masternak, PhD

Organization: University of Central Florida

Summary: Alzheimer's disease (AD) is the sixth leading cause of death in the United States, and the mechanisms responsible for AD remain poorly understood. The role of sex in AD seems to represent important factor, as women are of greater risk for developing AD. However, the detailed mechanism of this dependency is not well understood. Since aging is the leading risk factor for AD/AD Related Dementias (ADRD), and life expectancy for women is longer than for men, it would strongly suggest that lifetime risk of AD related dementia is greater for women than for men. Despite longer life expectancy, half of a woman's lifespan is during non-reproductive age. Based on this, researchers could ask if there is any contribution of hormonally inactive ovaries to organismal health and cognitive function. Researchers believe, ovaries can be the source of ovarian signaling factors involved in promoting health span. Previous studies demonstrated that transplanting young ovaries into old mice increases health span and lifespan with concomitant improvement of cognitive health after ovarian transplant. These novel findings indicate that young ovarian tissue can provide factors that slow/reverse the aging process and may prevent the onset of AD/ADRD. Researchers also showed that motor function (tremor amplitude and grip strength), cognitive behavior and sensory function were improved in old female mice by exposure to young ovarian tissues/cells. Interestingly, this positive influence was independent of hormone producing follicles and estradiol levels. Based on these newest findings, the researchers propose a novel hypothesis that ovarian somatic cells secrete circulating factors promoting healthy aging and protection from AD. To test this hypothesis, the research team will use procedures including transplantations of ovarian tissue and cells, and treatments with ovarian derived exosomes to evaluate putative novel ovarian-derived factors promoting cognitive health and protection against Alzheimer's disease.

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

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

13. **Grant #:** 24A13

Principal Investigator: Jeremy Grant, PhD

Organization: University of Florida

Summary: Black and Hispanic/Latino Americans are disproportionately affected by Alzheimer's disease and related disorders. Racial/ethnic differences in the risk of developing Alzheimer's disease are often attributed to social determinants of health (SDOH), which refers to how the conditions in which people live, learn, work, and play can affect a wide range of health outcomes. Most research on the relationship between SDOH and the risk of developing Alzheimer's disease has focused on various factors at the individual level, such as a person's level of education, income, and access to healthcare. A different approach that has gained more attention in recent years is examining SDOH at the contextual level, exploring how various features of a person's environment can contribute to their risk of developing Alzheimer's disease. Research has shown that older adults who live in disadvantaged neighborhoods have a greater risk of Alzheimer's disease than those living in more affluent neighborhoods. In addition, older adults living in rural areas are at higher risk of developing Alzheimer's disease than those in urban areas. Of particular interest are measures that integrate several different SDOH, which can allow researchers to examine the extent to which living in a specific neighborhood is associated with certain health outcomes. One such measure is the Area Deprivation Index (ADI), which integrates information about 17 aspects of SDOH to provide national and state-wide rankings of neighborhood disadvantaged for every census block in the United States. Research using the ADI has shown that living in a disadvantaged neighborhood is associated with a higher prevalence of chronic diseases such as high blood pressure, high cholesterol, and diabetes, which in turn increase the risk of cognitive decline and developing Alzheimer's disease or other forms of dementia. Furthermore, a growing body of research has shown that neighborhood-level disadvantage is related to cognitive function over time and biomarkers of Alzheimer's disease, such as brain size and cellular changes. However, more research is needed to understand how individual and contextual-level factors interact in Florida's diverse population, including people living in rural areas, people from diverse racial/ethnic groups, and people with limited English language skills. The proposed study will examine the relationships among neighborhood disadvantage, cognitive function, and biomarkers of Alzheimer's disease using data from the 1Florida Alzheimer's Disease Research Center (1Florida ARDC). The 1Florida ADRC is uniquely positioned to investigate these relationships, given the availability of various biomarkers of Alzheimer's disease in people examined across multiple years, particularly individuals from Black and Hispanic/Latino communities in Florida. Understanding these relationships can help inform public health strategies, interventions, and policies to reduce health disparities and promote brain health in underserved populations.

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 #:** 24A14

Principal Investigator: Abbas Babajani-Feremi, PhD

Organization: University of Florida

Summary: Dementia with Lewy bodies (DLB) is an Alzheimer's disease related dementia (ADRD) and part of Lewy body dementia, the second most common form of neurodegenerative dementia. DLB is often misdiagnosed or overlooked due to symptom overlap with other dementias, particularly Alzheimer's disease (AD). This results in delayed interventions and suboptimal outcomes for affected individuals, highlighting the need for early and accurate diagnosis of DLB. However, reliable biomarkers for DLB pathology are currently lacking, and the underlying mechanisms of core DLB features, such as cognitive fluctuations (CF), remain poorly understood. This project aims to address these significant clinical and scientific gaps by developing biomarkers for the early identification of DLB and investigating the brain areas and networks involved in CF in DLB. To achieve these goals, the project will utilize magnetoencephalography (MEG), an advanced brain imaging technique, and machine learning algorithms. MEG provides excellent spatial resolution (< 5 mm) and temporal resolution (< 0.2 ms), enabling researchers to obtain detailed information about brain activity related to cognitive fluctuations in DLB. By analyzing MEG data, the project aims to develop novel biomarkers that can differentiate individuals with DLB from those with AD at early disease stages. The project will also investigate the dynamic nature of the brain network in DLB using a technique called dynamic functional connectivity analysis. This approach allows research staff to understand how different brain regions interact and how these interactions change over time. By studying the aberrant brain network associated with cognitive fluctuations in DLB, researchers can gain insights into the underlying mechanisms of this condition. The project will be conducted at the Norman Fixel Institute for Neurological Diseases, a renowned research center for DLB. The institute has state-of-the-art facilities, including a top-of-the-line MEG scanner, which will be used to integrate MEG into the DLB research program. The project involves collaboration between experts in MEG, DLB research, and biostatistics, fostering a multidisciplinary approach to address the challenges posed by DLB. The outcomes of this project have the potential to significantly improve the early diagnosis and management of DLB, leading to better outcomes and quality of life for individuals affected by this devastating neurodegenerative disorder. By understanding the brain areas and networks involved in cognitive fluctuations, researchers can develop targeted interventions and therapies for DLB. The project also contributes to the advancement of scientific knowledge by filling important gaps in the understanding of DLB pathology and its underlying mechanisms.

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 #:** 24A15

Principal Investigator: Carla Fisher, PhD

Organization: University of Florida

Summary: Dementia is a brain disease that causes a decline in a person's memory and thinking affecting everyday life. Dementia can be due to various medical problems, including Alzheimer disease, Lewy body disease, and stroke. Individuals with these disorders rely on family caregivers to support them in both clinical and home care settings. Caregivers manage complex challenges, and caregiving impacts their quality of life. Communication is critical to facilitating their caregiving role and navigating the complexities of dementia care, including healthcare decision making. Dementia family caregivers could benefit from interventions that help develop skills to enhance their communication with healthcare providers and family members. Such interventions for caregivers in other disease contexts have also reduced caregivers' distress and burden. Further, online interventions offer caregivers a feasible way to develop their skills. In this study, the research team will collect the necessary data to adapt an online cancer caregiver education program called Healthy Communication Practice to make it specific to dementia caregivers' needs. The program utilizes evidence-based, authentic caregiver narratives as behavior modeling tools to teach communication skills in three contexts of communication that are central to the caregiving role: online communication (searching for credible health information and communicating with others about that information); communication with clinicians (advocating for care and navigating triadic communication in clinical settings); and communication within families (cultivating open, supportive communication). To effectively adapt the intervention from cancer to dementia and promote implementation success, a qualitative design is needed to capture the distinct situations of dementia caregiving. In doing so, researchers also ensure the stakeholders' voice—dementia family caregivers—is prioritized in identifying communication challenges and skill needs in each communication context. In Year 1, the research staff will interview two groups of family caregivers which will also increase the ability to adapt the intervention based on relationship type. The research team will conduct individual interviews with 30 caregivers representing two familial types: 15 adult children caring for a parent with ADRD and 15 caregivers of a spouse with ADRD. Researchers will then thematically analyze the interview data to identify key intervention development outcomes (challenging situations and communication skill needs) in each communication context addressed in the intervention (online, clinical, and family communication). In Year 2, the research team will continue to analyze data and disseminate findings as researchers adapt the intervention. Interview data will provide narratives that can be translated into behavior modeling tools (caregiver narratives) addressing common situations facing dementia caregivers that caregivers can relate to while learning critical communication skills. The research team will develop narrative behavior modeling tools for each communication context in Healthy Communication Practice, which will foster caregivers' acceptability and engagement with the adapted intervention. Study results will allow the research team to develop the adapted intervention in partnership with instructional design experts prior to testing it with a

larger population of Florida caregivers. Ultimately, this supportive, accessible resource can help support dementia caregivers' communication skill needs and promote healthy outcomes across the disease and care continuum.

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 #:** 24A11

Principal Investigator: Mary Holschbach, PhD

Organization: Nova Southeastern University

Summary: Researchers have yet to discover a cure for Alzheimer's disease (AD), and the currently available and newly approved medications only improve disease outcomes for a small fraction of AD patients (e.g. ~5% for Aduhelm). Therefore, researchers urgently need to identify protective factors and non-pharmacological interventions, especially for women who are at a two-times greater risk for developing AD. Some reports indicate that mothers are less likely to develop dementia, but because these data are correlational, it's unclear whether this is a direct connection or due to other related factors such as marital status, wealth, or overall health. Interestingly, controlled experiments in rodents have shown that reproduction and maternal experience acutely affect many hallmarks of AD, such as learning and memory, mood and emotion, and even plasticity and function of the hippocampus (a brain region strongly implicated in AD). Therefore, the research team hypothesizes that reproduction and motherhood directly modify disease risk and progression. Research staff will first test this in an experiment by measuring neural and behavioral hallmarks of dementia in female mice with or without prior reproductive/maternal experience. These maternal and reproductively naïve mice will be either "wildtype" mice undergoing normal aging or transgenic mice developed to model AD. Transgenic AD mice have diminished cognitive performance compared to wildtype mice and show neural signs of disease. The researchers hypothesize that reproductive/maternal experience will reduce neural and behavioral signs and symptoms of dementia in AD mice, making them more closely resemble the wildtype mice. This would demonstrate that parenting is an important factor that ameliorates disease risk. Just as motherhood may reduce risk for AD, interacting with children later in life by grandparenting or participating in intergenerational programs seems to benefit elderly patients with dementia. However, social engagement with young mice has never been tested as a behavioral intervention in rodent models of dementia, which precludes study into the biological mechanisms underlying benefits. Moreover, it may be more beneficial to some patients than others (e.g. parents versus nonparents). The research team will test this in a second experiment using older transgenic AD mice with or without prior reproductive/maternal experience. The researchers will expose half of the subjects to foster pups daily to test whether pup contact mitigates signs and symptoms of dementia. Because the researchers hypothesize beneficial effects of both parenting and interacting with unrelated

juveniles after aging, research staff expect that mothers will show fewer signs and symptoms than nonparents and that pup exposure will reduce neural and behavioral features of dementia. The strength of the effects of pup contact during aging may be stronger in mothers, which would suggest that the researchers should target intergenerational programming toward parents when opportunities are limited. This project will provide empirical evidence as to the protective effects of prior parenting and the beneficial effects of later contact with young and empower pursuits of federal funding to continue this line of work into the mechanisms of both protection and symptom mitigation. This will, in turn, revitalize and bolster the use of intergenerational programs in the care of aging patients in Florida and more broadly.

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 #:** 24A17

Principal Investigator: Rosie Curiel Cid, PsyD

Organization: University of Miami Miller School of Medicine

Summary: The Center for Cognitive Neuroscience and Aging (CNSA) has a robust and growing program of state and federally funded research devoted to developing novel diagnostic assessment paradigms and tools to detect preclinical Alzheimer's disease (AD) and AD-related disorders (ADRD) in culturally diverse older adults. Moreover, the CNSA is a Clinical Core site for the newly awarded 1Florida Alzheimer's Disease Research Center (1FL ADRC), a state-funded University of Miami Memory Disorders Clinic, and several longitudinal National Institutes of Health (NIH) research project grant program (RO1) projects that focus on AD and ADRD. This rich training environment, where the majority (>60%) of the population studied and served include individuals from historically underrepresented cultural groups, has been as the platform upon which the researchers have successfully and continuously trained Ed and Ethel Moore Postdoctoral Research Fellows since the program was initiated during the 2015-2016 year. The Postdoctoral Fellowship in Neuropsychology and Cognitive Neuroscience will offer a promising candidate the opportunity to receive specialty training in Alzheimer's disease by: developing enhanced clinical evaluation and diagnostic skills, participating in ongoing clinical research projects that are studying promising new methodologies to improve the clinical assessment of diverse older adults at risk for the development of AD and related disorders, learning about neuropsychological assessment and the development of diagnostic assessment instruments, which is of critical relevance in Florida and receiving training in writing federally funded grant applications to prepare the postdoctoral fellow to become an independent investigator. Competent clinical assessment that is sensitive to detect preclinical AD remains a critical priority area in Alzheimer's disease research. Offering this training opportunity to a neuropsychologist is of particularly high impact, in that this discipline plays a direct and critical role in Alzheimer's disease clinical research. In addition, the longitudinal nature of the research program will offer

the unique opportunity for the fellow to assist with longitudinal data analysis, expose them to state-of-the-art cognitive assessment methods and various biological markers of AD pathology including amyloid and tau neuroimaging and cerebrospinal fluid markers.Drs. Rosie Curiel Cid and David Loewenstein, would serve as primary and secondary mentors, respectively. Together, doctors Loewenstein and Curiel-Cid are leaders of the 1FL ADRC, and have multiple longitudinal RO1 studies (Loewenstein-PI and Curiel-PI) funded by the National Institute on Aging focused on studying culturally diverse older adults at risk for AD and related conditions. This focused and highly productive program of research at the CNSA, along with the mentors' longstanding background in training post-doctoral fellows and junior faculty, offers an unparalleled specialty training opportunity for the postdoctoral candidate to expand their competency to serve diverse older adults who are at risk for the development of neurodegenerative conditions.

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 #:** 24A18

Principal Investigator: Holly Cukier, PhD

Organization: University of Miami

Summary: Research has identified dozens of genes and loci associated with Alzheimer's disease (AD), but how these genes contribute to disease risk and the underlying mechanisms that drive disease is still being deciphered. The research team has previously identified the tetratricopeptide repeat domain 3 (TTC3) gene as a novel AD risk factor. TTC3 encodes an E3 ubiquitin ligase that acts in AD related pathways including protein kinase B (Akt) signaling, negative cell cycle control, and neuronal differentiation. These pathways are intertwined with normal neuronal and synaptic function, as well as amyloid beta (Aβ) and tau processing, hallmark features of AD pathology. In addition, lower TTC3 levels are seen in the brains of affected individuals, suggesting that expression may be negatively correlated with AD neuropathology, and that TTC3 could play a protective role. Micro ribonucleic acidss (miRNAs) are small, noncoding RNAs that typically inhibit coding RNAs. Naturally occurring circular RNAs (circRNAs) can act as sponges for miRNAs, titrating them away from their endogenous targets. Thus, circRNAs add another layer of complexity to gene regulation. Recently, a TTC3-specific circular RNA circ-0008572 was identified that binds miR-15b, an AD biomarker consistently downregulated in the blood of AD cases. Established targets of miR-15b include beta-secretase 1 (BACE1), which encodes a secretase that cleaves amyloid-beta precursor protein (APP), and nuclear factor kappa B subunit 1 (NF-kB1) and Ikappa kinase (IKK-a), which are involved in the inflammatory response. Based on genetic data and this regulatory evidence, the researchers hypothesize that TTC3 may influence AD pathogenesis through multiple mechanisms including its role as an E3 ubiquitin ligase and regulating the AD biomarker miR-15b. To clarify the roles

of TTC3 and miR-15b, the researchers propose the following aims: Delineation of the cellular and transcriptional consequences of TTC3 and examination of the role of TTC3 in regulating miR-15b.The induced pluripotent stem cells (iPSC) lines will be used to evaluate the production of the TTC3 circRNA and regulation of miR-15b. Modulation of the circRNA and miR-15b by siRNA silencing and miRantagonism, respectively, followed by transcriptional analysis will be used to identify novel interactions, targets, and pathways, and refine the understanding of the role of each of these components in AD pathogenesis. The researchers have generated iPSC from three AD patients with the TTC3 p.S1038C risk variant, as well as clustered regularly interspaced short palindromic repeats (CRISPR) edited homozygous p.S1038C isogenic iPSC lines. These cells will be grown into two-dimensional (2D) cortical neuronal cultures and evaluated for cellular phenotypes (e.g.: neurite outgrowth and migration), AD-related phenotypes (e.g.: intracellular pTau), and response to stress induced by either Ab fibrils or glutamate (excitotoxicity) exposure. The stability and direct interaction of TTC3 with its established ubiquitination targets, (e.g.: protein kinase B (AKT), deoxyribonucleic polymerase subunit gamma (POLG), smad ubiquitination regulatory factor 1 (SMURF2)), will be assessed. The downstream pathways will be investigated using CRISPR inhibition and activation of TTC3. The isogenic iPSCs will also be differentiated into three dimensional (3D) forebrain organoids to mimic the complex brain environment and characterized at the cellular and transcriptional level via single cell RNA-seq to delineate cell type-specific transcriptional profiles. In addition, 3D forebrain organoids will be derived from isogenic iPSCs in which components of the TTC3 circRNA–miR-15b pathway are modulated. These organoids will be analyzed for the cellular and molecular consequences.

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 #:** 24A19

Principal Investigator: Thomas Caulfield, PhD

Organization: Mayo Clinic Florida

Summary: The lack of deep binding sites of target and thus "undruggable" by traditional small molecule inhibitors is a long-standing challenge in the field of drug discovery. An example of such an "undrugabble"-difficult target is amyloid-beta (Aβ) whose aggregation is widely regarded as a pathogenic initiator of Alzheimer's disease (AD). It is pivotal to clearance of Aβ aggregation/deposition in order to delay or even halt AD. This clearance can be accomplished by the development of an innovative new strategy in drug discovery known as targeted protein degradation. This research method aims to completely eradicate these problematic proteins. Using the body's own natural "garbage disposal system," known as the proteasome, these drugs designate these proteins for destruction and then send them off to be recycled within the cell. This is accomplished by co-opting the body's own natural "garbage disposal system."

During a process known as ubiquitination, a molecule called ubiquitin will attach itself as a tag to this protein, which is done by E3 ubiquitin ligase, which is followed by degradation. Only after this will the protein be eligible for disposal in the trash compartment of the cell. The fact that not all proteins are able to simply attach themselves to the E3 ubiquitin ligase that is in charge of adding ubiquitin presents a problem for this essential process. In order to get over this obstacle, specialized small molecule medications that function as "molecular glues" are being developed to assist enzymes in "sticking" more effectively to their targets. Molecular glues are a specific category of molecules that have the ability to bring together two proteins that, under normal circumstances, would not interact with one another. The discovery and creation of molecular glues present considerable hurdles; nonetheless, this modality holds immense promise; hence, the researchers focus on the job of involving artificial intelligence-driven platforms. When researchers think about the purpose of molecular glue, which is to link one protein to another, research staff locate the molecule that not only binds one protein but also produces such configurational modifications that this protein will stick to another one. The application of artificial intelligence (AI) in this context could prove to be incredibly useful, contributing to the development of new paradigms for the design of molecular glues. Here, the researchers propose to use a deep graph neural network model to design potential molecular glues that help amyloid beta protein and E3 ligase protein stick together in a way that changes the fate or function of the target protein. Using this method, the research team will be able to predict the surface features of proteins and choose E3 ligases that work well with the amyloid beta targets for the degradation which are seen as a potentially effective therapeutic strategy against Alzheimer's disease. The researchers also aim to build E3 ligase-biased molecular glue libraries for deleterious amyloid beta based on structural biology insights and screening data.

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 A: Newly Awarded Active Grant Details
Funded Fiscal Year 2022-2023

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
23A01	Florida International University	Giri Narasimhan, PhD	$99,783.00	2/28/2025	No	No	No
23A02	Florida State University	Julia Sheffler, PhD	$350,000.00	2/28/2027	No	No	No
23A03	Mayo Clinic Jacksonville	Yunjung Jin, PhD	$100,000.00	1/31/2025	No	No	No
23A04	Mayo Clinic Jacksonville	Wilfried O Rossoll, PhD	$350,000.00	1/31/2025	No	No	No
23A05	Nova Southern University	Sibel Antonson, DDS, PhD, MBA	$99,459.00	6/30/2024	No	No	No
23A06	University of Central Florida	Susanny Beltran, PhD, MSW	$99,883.00	2/28/2025	No	No	No
23A07	University of Central Florida	Jihe Zhao, PhD	$350,000.00	2/28/2027	No	No	No
23A08	University of Florida	Stephen Anton, PhD	$350,000.00	2/28/2025	No	No	No
23A09	University of Florida	Jie Xu, PhD	$350,000.00	1/31/2026	No	No	Yes
23A10	University of Miami	David Loewenstein, PhD	$349,983.00	2/28/2025	No	No	No
23A11	University of Miami	Philip Harvey, PhD	$99,345.00	2/29/2024	No	No	No
23A12	University of Miami	Oliver Bracko, PhD	$350,000.00	1/31/2026	No	No	No
23A13	University of Miami	Tatjana Rundek, MD, PhD	$100,000.00	1/31/2024	No	No	Yes
23A14	University of Miami	Roger Leblanc, PhD	$52,536.00	5/31/2024	No	No	No
23A15	University of Miami	Elizabeth Crocco, MD	$349,102.00	2/28/2025	No	No	No
23A16	University of Miami	Rosie Curiel Cid, PsyD	$349,912.00	3/31/2025	No	No	No
23A17	University of Miami	Claes Wahlestedt, MD, PhD	$349,995.00	2/28/2026	No	No	No
23A18	University of South Florida	Hongdao Meng, MD, MPH, PhD	$350,000.00	2/28/2027	No	No	No

1. **Grant #:** 23A01

Principal Investigator: Giri Narasimhan, PhD

Organization: Florida International University

Summary: The project has just gotten underway starting in Spring 2023, and no preliminary results will be available until the samples are processed and analyzed. Over 45 million people aged 65 and older worldwide have Alzheimer's Disease (AD) Florida's aging population has created a considerable disease burden. Current treatments for symptomatic AD show modest benefits for cognition but little or no impact on the progression of AD. Research staff expect the results of this research to impact this population of Floridians suffering from AD. The proposed investigation explores the development of the presence of microbial genetic material as a novel blood biomarker for the detection and/or progression of AD. More importantly, the project also includes a causal analysis component, which could help pinpoint potential causative agents or triggers of AD initiation and/or progression.

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 #:** 23A02

Principal Investigator: Julia Sheffler, PhD

Organization: Florida State University

Summary: Research staff have created the Integrated Science for Healthy Aging Participant Registry in preparation for focus groups and the clinical trial. Thus far, research staff have created Standard Operating Procedures and completed training with research assistants to recruit participants into the repository. Currently, 151 older adults have been recruited to join. In addition to ongoing recruitment efforts, research staff have completed transcribing of qualitative data from exit interviews and have almost competed coding this data as well. This qualitative data is currently being used to update the intervention program materials and design. Previously collected qualitative data will be combined with focus group feedback to finalize the intervention for the clinical trial. The project principle investigator (PI) has also recently hired a full-time research coordinator for the lab who will be providing additional assistance on this project in preparation for the clinical trial.

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 #:** 23A03

Principal Investigator: Yunjung Jin, PhD

Organization: Mayo Clinic Jacksonville

Summary: Alzheimer's disease (AD) is a growing public health crisis in Florida, and accumulating studies show that Lewy pathology is one of the most common co-pathologies in AD. Alpha-synuclein (α-SYN), encoded by α-synuclein (SNCA) gene, is the primary component of Lewy pathology such as Lewy bodies (LB) and Lewy neurites (LN), which drives neurodegeneration. More than half of AD brains present with concomitant Lewy pathology at autopsy, suggesting that α-SYN aggregation is a regulated event in AD pathogenesis. Work has shown that α-SYN seeds are detected in postmortem AD brains even without detectable Lewy pathology. Moreover, the amplified α-SYN aggregates from AD brains were toxic to human induced pluripotent stem cells (iPSC)-derived neurons. The researchers, therefore, hypothesize that the seeding and aggregation of α-SYN is one of the key events in the pathogenesis of both AD and LBD (Lewy body dementia), and targeting this pathway has therapeutic potential to prevent or delay the disease onset and progression. In this proposal, the research team aimed to develop a novel synucleinopathy model system using human iPSC-derived cerebral organoids and neurons, and to discover potential drug candidates to inhibit α-SYN aggregation

using this model. Specifically, the research team generated cerebral organoids and neurons using the iPSC lines from individuals carrying SNCA triplication and from normal controls. The α-SYN pathological features such as α-SYN phosphorylation and aggregation was assessed in these organoids and neurons. Interestingly, both organoids and neurons carrying SNCA triplication showed higher levels of insoluble α-SYN aggregates compared to control ones. To understand the molecular mechanisms related to α-SYN pathology in this model and the relevance to human diseases, the research team performed single cell RNA sequencing (scRNA-seq) with organoids. Research staff found that excitatory neuron clusters mainly expressed higher levels of SNCA genes, indicating that synucleinopathy occurs mainly in excitatory neurons. During next period, researchers will perform pathway analysis to figure out the critical signaling pathway related to synucleinopathy in AD. Single nuclei ribonucleaic acid sequencing (snRNA-seq) will also be performed using the postmortem AD, LBD, and SNCA multiplication human brains to compare the similarities and differences of the molecular pathways between human brains and organoids. Researchers will then screen Food and Drug Administration (FDA)-approved drug library to identify drug candidates that can inhibit α-SYN aggregation using the real-time quaking induced conversion (RT-QuIC) assay. Overall, this project will enable the discovery of potential drugs that can inhibit α-SYN seeding activity using human iPSC-derived models, providing a great opportunity to identify and develop highly applicable therapeutic strategies targeting α-SYN aggregation for AD and LBD.

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 #:** 23A04

Principal Investigator: Wilfried O Rossoll, PhD

Organization: Mayo Clinic Jacksonville

Summary: Alzheimer's disease (AD) is a condition known for the accumulation of tangled proteins in the brain, causing memory loss and other symptoms. These tangles, called neurofibrillary tangles (NFTs), are a key feature of the disease. Scientists are researching ways to stop or reverse this process to develop new treatments. Recent studies have found that certain proteins called importins can help prevent the formation of these protein tangles. Importins mediate the transport of proteins into the cell nucleus but also have a unique ability to act as "molecular chaperones," which means it can help tangled proteins to return to their normal state. This discovery opens up a promising avenue for developing treatments for AD and similar disorders. To investigate this further, researchers are using advanced lab techniques to understand how importins work in detail and to figure out how importins make the tangled proteins more soluble, prevent nerve cell damage, and contribute to the disease. Ultimately, this knowledge could lead to new strategies for treating Alzheimer's disease. The goals of the research are: to learn how importins restore the normal state of tangled proteins in the lab, to

see how importins protect nerve cells in both cell cultures and animal models, and to explore the connection between importins and the protein tangles in the brains of people with Alzheimer's disease.

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

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

5. **Grant #:** 23A05

Principal Investigator: Sibel Antonson, DDS, PhD, MBA

Organization: Nova Southern University

Summary: Quality, consistency and predictability of long-term oral-healthcare (OH) significantly improves quality of life (QOL) for patients with Alzheimer's disease(PAD), and reduces the healthcare system burden by preventing chronic dental diseases, such as periodontitis and caries. These diseases result in devastating outcomes leading to painful inflammatory and degenerative oral diseases. It is also shown that there is a link between periodontal disease and AD. Also, a 24% increase in PAD population is expected by 2025 in Florida. Therefore, it is critical to develop a new intervention strategy that will provide a sustainable and achievable OH maintenance program, thereby reducing this significant risk factor, slowing cognitive decline for PAD, and increasing QOL for PAD. PAD have multiple OH problems due to loss of manual dexterity, daily OH routines, and xerogenic medications. Training caregivers in OH implementation has been successful; however, long-term maintenance and sustainability of consistency has been a challenge. Along with the administration of daily OH, topical chlorhexidine(CHX) is used in dentistry as an antibacterial agent to control periodontal disease, and caries control in high-caries risk patients. It requires patients' cooperation to swish the CHX solution in their mouth for 30 seconds, then spit out, twice daily. Compliance is low, even for healthy patients due to application time, unpleasant taste, and staining of the dental hard tissues. An alternative varnish delivery system that can be applied by a dentist or dental professional can eliminate the need for patient compliance. Also, fluoride varnish can be applied along with the CHX to reduce caries lesions. The objective of this study is to assess if CHX and fluoride application in a varnish form can provide a sustainable improvement in PADs' periodontal and caries status. Additionally, patients' cognitive status will be assessed to test if there is a correlation between the maintenance of OH and the rate of cognitive decline. In partnership with the Alzheimer's Association Florida Region (AAFR), the researchers will enroll 165 PAD for a six month OH intervention. Participants will have a series of cognitive assessments, a dental examination, and saliva collection to investigate the base protein levels to identify inflammatory and AD biomarkers, prior to being randomly assigned into three groups: a group which will receive debridement, toothbrushes, and care instructions for their teeth; a group receiving additional CHX and fluoride varnishes; and a control group that will not have dental health intervention. At three and six months, the same cognitive, biological, and dental

health tests will be conducted. If evidence indicates that the newly developed dental health intervention is successful, groups 1 and 3 will be given the opportunity to receive it. This work aligns with the Florida Department of Health's (FDOH) priority of developing treatments for PAD through interprofessional partnerships. The research team expects to establish an implementable, sustainable OH protocol to prevent periodontal disease and caries, and slow cognitive decline for the PAD. In partnership with the AAFR, a larger community outreach effort will be performed to increase dental health in the Florida PAD population based on successful findings from this work.

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

Collaborations: This project is a collaboration between Nova Southeastern Univiersity's (NSU) Colleges of Dental Medicine (CDM) and Psychology (COM). A PhD student from the COM is a member of the research team. Additional students and faculty members are planned to join the team from both Colleges. NSU is located in Fort Lauderdale, FL

Journals: None at the time of reporting.

Patents: None at the time of reporting.

6. **Grant #:** 23A06

Principal Investigator: Susanny Beltran, PhD, MSW

Organization: University of Central Florida

Summary: The research team completed qualitative interviews with key informants which constitute Aim 1A of the research project. The interviews explored nursing home administrative staff's current processes for identifying residents with dementia appropriate for end-of-life discussions and transitions, and sought their input related to the proposed use of the advanced dementia prognostic tool (ADEPT) as a tool to standardize this process. The research team is finalizing the analysis of the qualitative transcripts and engaged in analysis of the demographic details collected via online surveys. The findings of the qualitative analysis will help describe current processes used in nursing homes, perceived barriers, and suggestions that will guide the design of the care process intervention and fidelity instruments to be used in Phase 2/Aim 2. These findings were disseminated in November in Tampa, at the Gerontological Society of America's Annual Scientific Meeting (GSA). GSA is the largest interdisciplinary organization devoted to research, education, and practice in the field of aging, and well-respected internationally and nationally. The presentation described current processes shared by participating nursing homes to identify residents with dementia appropriate for end-of-life care planning, highlight potential flaws associated with current processes, and generate ideas for care process improvements. The research team has also begun to develop a draft of the intervention protocol based on Aim 1A findings (Aim 1B/Phase 1), to be shared with the site coordinator for input prior to implementation. The research team is also developing the fidelity instrument that will be used for the intervention. Furthermore, the research team is writing an update to the institutional review board (IRB) application, to receive approval for the next phase of the research project. This is required since the details of phase 2 could not be provided to

IRB initially, due to them being contingent upon Phase 1. Immediate next steps include obtaining IRB approval for phase 2, finalizing the implementation protocol and fidelity instrument, and onboarding the site coordinator prior to beginning the intervention pilot.

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 #:** 23A07

Principal Investigator: Jihe Zhao, MD, PhD

Organization: University of Central Florida

Summary: This project was initiated and became active officially on March 23, 2023. Immediately after that, the research team started setting up the experimental systems proposed including both the patient-derived three dimensional (3D) mini brains and the mouse models that recapitulate the patient conditions. The research team is in the early phase of the project and has progress as planned. The pathohistological hallmarks of AD are two folds including the plaques, inter-neuronal amyloid b protein (Ab), and neurofibrillary tangles, intra-neuronal accumulation of hyperphosphorylated tau. However, current therapies targeting these two hallmarks are not effective, indicating that they may not directly cause AD. Thus, further investigating the cellular and molecular mechanisms of AD underlying its relationship with the pathology of Ab and tau is needed. This project is focused on Krüppel-like factor 8 (KLF8), a transcription factor gene known to be lost in the patient brain. The job of a transcription factor is to turn on or turn of expression of other genes. Although KLF8 turns on and off many genes critical for learning and memory in the adult brain, its role in AD pathology has not been investigated due to the lack of proper animal models. The research team developed novel mouse models where the research team can manipulate KLF8 expression in the neurons. The preliminary data demonstrated that loss of KLF8 caused the neuronal death and cognitive decline. The data also showed that the loss of KLF8 caused dysregulation of genes critical for maintaining cognitive function and a normal brain environment and for preventing abnormal tau phosphorylation. These results strongly suggest a role for KLF8 in the protection of neurons and loss of KLF8 function in the neurons may involve the pathological progression of AD. The research team proposes to investigate the role of KLF8 in tau pathology in AD using the novel mouse models and a patient disease mimicking mouse model as well as AD recapitulating 3D mini brain to be created in tissue culture. Completion of this project will significantly advance understanding of the mechanisms underlying AD pathology and lift a great hope for developing effective therapy for the patients.

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 #:** 23A08

Principal Investigator: Stephen Anton, PhD

Organization: University of Florida

Summary: During the past six-months, the research team initiated participant recruitment, screening, and enrollment efforts. The research team also developed study intervention materials. Specifically, the research team sent mass mailings of postcards, as well as a newsletter which described the fasting enhance study to the participant registry. These efforts result in incoming calls of interest from a total of 147 individuals. Of these, 116 did not qualify to move to the next screening phase per the online prescreen (88) or the phone screen (28). A total of nine individuals were, however, eligible and of these seven have qualified to participate in this study based on the in-person screening visit. There is one individual scheduled for an in-person screening visit, and one participant to be scheduled. Additionally, there are approximately 22 individuals that the research team is trying to reach to complete phone screenings. The research team initated the intervention in November of 2023.

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 #:** 23A09

Principal Investigator: Jie Xu, PhD

Organization: University of Florida

Summary: Alzheimer's disease (AD) is a complex condition with a wide array of causes, triggers, risk factors, clinical presentations, severity levels, and responses to treatment. This complexity is reflected in the diverse ways the disease progresses in different individuals, resulting in various subtypes of AD progression. Understanding these distinct AD progression pathways, along with the factors influencing them, from clinical attributes to social determinants of health (SDoH), is crucial for gaining insights into the disease's underlying mechanisms and for developing more precise and effective treatment approaches. The advent of large clinical research networks (CRNs) and the availability of real-world data (RWD) from electronic health records (EHRs), coupled with advancements in machine learning, present a unique opportunity to enhance the ability to categorize different AD subphenotypes accurately. The research team aims to: develop computable phenotypes (CPs) and natural language processing (NLP) algorithms and tools to create high-quality RWD cohorts; derive trajectory patterns that depict the progression of patients to AD through federated machine learning (ML) algorithms, where each pattern represents a distinct subphenotype; identify the impact of AD risk factors on the

onset and progression of AD using a counterfactual explanation model; and quantify the causal effect of the identified risk factors on AD risk by measuring the average treatment effect across various AD subphenotypes.To accomplish these objectives, the research team will leverage access to extensive collections of RWD from the OneFlorida+ network, a CRN contributing to the national Patient-Centered Clinical Research Network (PCORnet). This network encompasses data from approximately 20 million patients across Florida, Georgia, and Alabama. Progress to date includes the establishment of a longitudinal RWD cohort of AD patients, which serves as the foundation for the research. The research team has developed a machine learning approach utilizing longitudinal EHR data to identify distinct progression pathways leading from mild cognitive impairment (MCI) to AD. The research team's methodology involves employing Long Short-Term Memory (LSTM) models and hierarchical clustering techniques. The research team validated the approach using data from two healthcare system sites randomly selected from the OneFlorida+ network. In both datasets, the research team identified multiple subtypes of patients with unique progression patterns from MCI to AD. This finding suggests that MCI is not a uniform disease state, and various subtypes of MCI patients may exist, each following a different trajectory toward AD. This outcome-oriented AD progression subtyping method not only captures disease progression transitions but also the longitudinal patterns in patient trajectories. It goes beyond focusing solely on clinical status, offering enhanced diagnostic and prognostic value. Additionally, it holds the potential of enabling tailored care planning for the benefit of Floridians.

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

Collaborations: None at the time of reporting.

Journals: Xu J, Wang F, Zang C, et al. Comparing the effects of four common drug classes on the progression of mild cognitive impairment to dementia using electronic health records. *Scientific Reports*. 2023;13(1). doi:10.1038/s41598-023-35258-6.

Patents: None at the time of reporting.

10. **Grant #:** 23A10

Principal Investigator: David Loewenstein, PhD

Organization: University of Miami

Summary: The purpose of this study is to examine the performance of older adults at risk for Alzheimer's disease (AD) and AD related disorders (ADRD) on novel cognitive challenge tests and relate these to promising imaging and plasma-based biomarkers sensitive to AD pathology and neurodegeneration. The early detection of AD and ADRD using sensitive screening tools is critical to ensure that individuals who may be at risk are identified during the earliest stages of these neurodegenerative conditions and referred to clinical trials or other interventions that can delay symptom onset. In south Florida, the research team is particularly dedicated to ensuring that these methods can be generalized to historically understudied individuals such as Hispanic/Latinos and Black/African American older adults, since Miami Dade County's residents from these cultural groups comprise approximately 70% of the population. In the reporting

period between March 1, 2023, and September 30, 2023, this Research Study has progressed as planned. Researchers successfully obtained full Institutional Review Board (IRB) approval and completed all study start-up activities during the initial months of the reporting period. This included hiring staff, training the study team on the protocol that includes comprehensive evaluations including phlebotomy, and neuropsychological testing. The database was set up using Research Electronic Data Capture (REDCap), the research team ordered, received, and organized all supplies needed to conduct the study procedures, and initiating and securing the intra-institutional resources to complete all aspects of the proposed work. Participant enrollment began during the first quarter of the project (July 2023). Since then, the researchers have enrolled 29 total participants (July to September 30, 2023) who have completed all planned procedures. Researchers also identified 37 additional eligible that researchers plan to schedule by the end of the calendar year. No issues have arisen with regards to consenting/enrolling, blood draws, performing neuropsychological assessments, or questionnaires. Importantly, researchers participated in 12 community events during the reporting period in both Miami Dade and Broward County to share information and education about this study, brain health, and engage persons from underrepresented communities in research. To that end, this project directly impacts Floridians by providing education about brain health, dementia prevention, and generating new science that can improve the early detection of AD and ADRD for Floridians. The project also serves as a training platform for graduate level students who are learning how to conduct both clinical research and provide clinical care to Florida's aging population.

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

Collaborations: Graduate students come from three postsecondary institutions which are the University of Miami, Nova Southeastern University, and Albizu University. The primary objective of these collaborations is to provide training to pre-doctoral practicum students in neuropsychological assessment of participants who enroll into the Innovative Cognitive, Plasma-Based and Extra-Cellular Free-Water as Early Biomarkers of AD study.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

11. **Grant #:** 23A11

Principal Investigator: Philip Harvey, PhD

Organization: University of Miami

Summary: A postdoctoral research fellowship was granted to Dr. Denise Carballea, a bilingual and bi-cultural post-doctoral fellow who is training to become a neuropsychologist with a specialty in Alzheimer's disease (AD) and AD related disorders (ADRD). Consistent with the regular academic cycle, Dr. Carballea began the training year on September 11, 2023. AD is a devastating condition that impacts the affected individuals and their families, as well as society. Age is the primary risk factor for AD, and the rapid aging of the population is expected to lead to an economic and public health crisis of immense proportions in the decades ahead. This research fellowship program is devoted to mentoring a qualified individual who desires to

pursue a career as a clinician-scientist in the field of AD/ADRD. The fellow has completed all training and onboarding activities and has been approved as a study team member by the Institutional Review Board. Dr. Carballea has readily integrated as a member of the Center for Cognitive Neuroscience and Aging (CNSA) team and the 1Florida Alzheimer's Disease Research Center (1Florida ADRC), and works productively with mentors, other trainees, and staff. The University of Miami Center for Cognitive Neuroscience and Aging (CNSA) and the large National Institutes of Health (NIH)-funded clinical research program there serve as the ongoing training environment for Dr. Carballea, as planned. This fellowship training year is focused on 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 for Dr. Carballea has included learning about various empirically supported intervention strategies to prescribe interventions that are personalized to the needs of the individual. Dr. Carballea is actively participating in didactic training lectures weekly (2023-2024 Neuroscience Didactic Lecture Series). This series is aligned with Houston Conference Guidelines for the training of specialty neuropsychologists. The fellow has been involved with the Principal Investigators and mentors to begin to develop an independent project that will be piloted in this Center. As it relates to leadership, Dr. Carballea is also participating in advancing the training of predoctoral students who are training in clinical research methods, and psychometry at the CNSA. In addition to the fellow's supervisory duties, Dr. Carballea is in training to lead the neuropsychological reporting during etiological consensus conferences and has taken on higher level junior faculty oversight of a longitudinal NIH grant under the guidance of Co-Mentor, Dr. Loewenstein. Impact to Floridians: There is an urgent need to adequately train the next generation of clinician-scientists that will contribute greatly to the health of older adult Floridians and their families. Specialists in the field of AD need to develop advanced clinical research skills to expand upon ongoing efforts aimed at the development of accessible diagnostic methods that could potentially detect AD before irreversible brain degeneration occurs. The current training opportunity is of particularly high impact, in that the field of neuropsychology plays a critical role in the diagnosis and management of AD/ADRD.

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 #:** 23A12

Principal Investigator: Oliver Bracko, PhD

Organization: University of Miami

Summary: Currently, 580,000 people live with Alzheimer's Disease (AD) in Florida, and many have increased inflammation in blood vessels, contributing to the disease's progression and severity. There is currently no cure or effective treatment for AD. As such, there is a dire need

for new research directions. The project aims to understand how inflammation in the body can harm the brain and lead to AD. The focusing on the role of blood platelets, a tiny cell in the blood that is known to clot blood after a wound but also causes blood vessel damage in AD. These platelets seem to be connected to memory problems in Alzheimer's patients, but researchers are not sure exactly how and when the cells are changing and how communicate with the brain. So far, the research team identified how to isolate proteins gently from platelets. The research team found that in mice with Alzheimer's, these platelets have more inflammation and more signal molecules that could trigger brain damage. This might be causing problems in the blood vessels and brain. In simple terms, research staff are getting closer to using advanced microscopy for research, and are learning more about why these platelets seem to be more active in AD. This project could help researchers find new ways to treatment options for Alzheimer's patients in the future and improve the lives of patients, families, and caregivers in Florida and the United States.

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 #:** 23A13

Principal Investigator: Tatjana Rundek, MD, PhD

Organization: University of Miami

Summary: This program invests in the development of the TRANSlational Fellowship Opportunity for Research on Multimorbidity in Alzheimer's Disease: TRANSFORM-AD, a one-year program for one fellow (MD or PhD) at the University of Miami leveraging experience in research training programs for over two decades. The overall goal of the program is to increase the number of diverse Alzheimer's disease and related dementias (ADRD) investigators and leaders in cross-disciplinary clinical translational research, who can effectively and rapidly translate, implement, and disseminate discoveries to practice and community. With an additional goal to address special health challenges and health disparities of the diverse ADRD patients served through team science and collaborations with community partners and diverse health care stakeholders. Dr. Sonya Kaur, selected from a large pool of eligible applicants in neurology, psychiatry, psychology, neuropathology, and neuroscience programs has a strong interest in brain and cognitive aging, multimorbidities, quality of life for aging adults and caregivers, and novel therapeutic approaches in ADRD. A junior faculty member, assistant professor in the Department of Neurology, Division of Neuropsychology was also selected. The training program will provide specific ADRD content education curriculum that incorporates multimorbidity, deleterious factors as well as protective factors such as physical exercise and healthy sleep hygiene, neuroimaging, and biomarkers; general research skills and tools, and immersion into research focused on cerebrovascular factors, and multimorbidities that accelerate cognitive decline. Additionally, Dr. Kaur will receive novel training in dissemination

and implementation science to learn skills/tools on disseminating research findings into valuable information to benefit patients, caregivers, and the community. The program is specifically designed to address health disparities in ADRD for the rapidly growing aging and diverse population of south Florida. The research team has been preparing Dr. Kaur for independence in ADRD research by providing the requisite knowledge and skills in biology of brain aging and ADRD, multimorbidity, health disparity, behavioral research, data science, drug discovery, intervention, and implementation science for rigorous and cutting-edge ADRD research. To date, Dr. Kaur has made strides as the new trainee. Researchers prepared a draft Individual Development Plan (IDP). The trainee met with the primary mentor and co-mentors to define and finalize the IDP. A K12 proposal in sleep disturbance and AD biomarkers in diverse Hispanic/Latino middle aged to older adults was submitted. This is one of the key performance indicators of this training program. A letter has been written/submitted of intent for the Alzheimer's Association Clinician-Scientist Fellowship and plans to submit an National Institutes of Health K award. The research team completed training in biostatistics and has attended training at the University of Pittsburgh in sleep and circadian science. The trainee enrolled in formal coursework in Design and Analysis of Human Genomic Studies and is preparing an analysis examining the association between polygenic risk score for sleep duration and cognitive decline. Dr. Kaur has also prepared manuscript proposals in sleep disturbance, vascular risk, and AD biomarkers in Hispanic/Latino older adults. One manuscript was accepted for publication in the area of sleep duration and brain volumes in Hispanic/Latinos in the top tier Alzheimer's disease journal, Alzheimer's Dementia.

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

Collaborations: Collaboration from March 5, 2023 – June 30, 2023 of this training grant included meeting with TRANSFORM-AD program mentors Dr. David Loewenstein and Dr. Rosie Curiel, also partners at OneFlorida Alzheimer Disease Research Center (1FL ADRC) and University of Miami (UM) Center for Cognitive Neuroscience and Aging (CNSA). Meetings were held to draft candidate search committee guidelines and deadlines and to consider additional search committee faculty members as well as to conduct the trainee search and to choose the final candidate. Collaboration continued once Dr. Kaur started as the TRANSFORM-AD Trainee on the development and finalization of her IDP. Dr. Kaur is also a member of Evelyn F. McKnight Brain Institute (EMBI), and has been developing a network of collaborations across the Institute as well as with other EMBI at the University of Florida, University of Alabama at Birmingham, and University of Arizona. From July 1, 2023 – September 30, 2023, collaboration on this training grant included meeting with TRANSFORM-AD program mentors Dr. David Loewenstein and Dr. Rosie Curiel, also partners at 1FL ADRC and UM CNSA and Dr. Kaur's statistical advisor, Dr. Hannah Gardener. These collaborations have been instrumental in fostering Dr. Kaur's work and growth on the IDP and as the TRANSFORM-AD Trainee. Since the inception of the grant, Dr. Kaur as a member of EMBI at UM, has worked to build upon a network of collaborations across the Institute as well as with the other McKnight Brain Institutes that the research team partner with.

Journals: González KA, Tarraf W, Stickel AM, et al. Sleep duration and brain MRI measures: Results from the SOL-INCA MRI study. *Alzheimer's Dement*. 2023; 1-11. doi:10.1002/alz.13451.

Mahanna-Gabrielli E, Kuwayama S, Tarraf W, et al. The Effect of Self-Reported Visual Impairment and Sleep on Cognitive Decline: Results of the Hispanic Community Health Study/Study of Latinos. *J Alzheimers Dis*. 2023;92(4):1257-1267. doi:10.3233/JAD-221073.

Patents: None at the time of reporting.

14. **Grant #:** 23A14

Principal Investigator: Roger Leblanc, PhD

Organization: University of Miami

Summary: Majority of the existing therapies are used as symptomatic treatments in Alzheimer's Disease (AD) and deal with one principal neuropathological hallmark at a time. Therefore, single modality of "One-molecule-one-target" strategies creates severe limitations for treating AD. On the contrary, restoring neurotransmitter levels by combined combinatorial inhibition of cholinesterases, and regulation of glutamate production, in conjunction with strategies to counter tau protein and beta-amyloid (Aβ) plaque accumulation, would constitute a therapeutically robust, multitarget approach. However, combination of the multiple drugs without any carrier is strictly limited by the chemical structure of the drugs and conjugation techniques. In addition, each of these drugs have an active site related to the efficiency towards AD. Therefore, combination of these drugs just by themselves terribly reduces the treatment effects. Traditional nanomaterials such as liposomes, dendrimers and metal-based particle have been applied for the treatment of AD as the nanocarriers. However, it has been shown that there are many challenges for the use of these traditional nanomaterials due to poor water solubility, high toxicity to the healthy tissue, deprived particle stability, and most importantly the lack of ability to cross the blood-brain barrier (BBB). As a novel nanomaterial discovered in 2000, Carbon Dots (CDs) have exhibited various properties. Most significantly, it was constantly observed that CDs could inhibit the formation of amyloid precursor protein (APP), Aβ, Aβ fibrils, and tau protein aggregates by diverse surface interactions. Additionally, CDs won't induce the generation of ROS in the dark, so the use of CDs won't cause oxidative stress or inflammation to the brain. Furthermore, CDs are promising drug nanocarriers considering thee biocompatibility, abundant surface functional groups, high surface area-to-volume ratio, small size, excellent photoluminescence, and most importantly the ability to cross BBB. In this study, the research team plans to benefit from abundant surface functional groups of CDs as "Combination-drugs-multi-targets" agents to combat AD. Briefly, CDs will be conjugated three different ligands to address the inhibition of cholinesterases, regulation of glutamate productions, up-regulation of nerve growth, tau protein and beta-amyloid plaque accumulations. These three drugs are tramiprosate, huperzine A and memantine. Among these drugs, tramiprosate binds to amyloid to prevent its conversion to beta-sheets and subsequent aggregation. In addition to the symptomatic, cognitive-enhancing effect via inhibition of acetylcholinesterase (AChE), several recent studies have reported that huperzine A has "non-cholinergic" effects on AD. Finally, memantine is meant to prevent excess glutamate from killing the nerve cells, without disturbing the normal transmission of nerve signals. Currently, there has been neither an ongoing nor finished investigation which incorporates four principal hallmarks of AD in addition with a premise to upregulate the neuronal cell growth. Therefore, this study holds great premises as a

powerful nanomedicine and drug nanocarrier with the capability to deliver three separate drugs across the BBB to inhibit the cholinesterases, glutamate productions, tau protein and beta-amyloid plaque accumulations while upregulating the nerve growth with higher efficacy than one molecule one target drug delivery system.

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 #:** 23A15

Principal Investigator: Elizabeth Crocco, MD

Organization: University of Miami

Summary: A critical gap in Alzheimer's disease (AD) and Alzheimer's disease related disorders (ADRD) clinical research is the vast under-under-representation of Black/African American (AA) older adults. Despite the pandemic, the staff has been able to develop an African American Registry in which over 100 participants have been enrolled and the intention is to meet the original goal of 120 participants during the awarded no-cost extension period. The researchers have conducted extensive baseline cognitive, neurological, and medical evaluations, have obtained comprehensive blood panels including fasting glucose, glycated hemoglobin (A1C), and complete lipid panel assessing comprehensive cardiovascular and metabolic risk factors as well as lifestyle measures including social and structural determinants of health. Importantly, over 70 percent of participants in the Registry have enrolled in National Institutes of Health (NIH) studies such as the 1Florida Alzheimer's Disease Research Center (1Florida ARDC) and several NIH funded longitudinal studies of aging. The researchers' vast outreach and community partnerships with stakeholders in the African American community make this proposal even more feasible, and the research team have an unprecedented opportunity to do more. In this proposal to expand the Registry, the research staff will recruit an additional 150 AA Registry participants to obtain plasma biomarkers that were not collected initially such as plasma-based biomarkers including p-tau217, plasma-based neurodegenerative biomarkers (Glial Fibrillary Acidic Protein [GFAP] and Neurofilament Light Chain [NfL]) and inflammatory markers. The data obtained for this registry will better characterize and expand upon the current database, that is flourishing. Promising plasma-based markers represent invaluable information that the institution and other Florida-based AD/ADRD investigators can access to further advance knowledge and answer critical scientific questions in understudied African American older adults. Ultimately, the important data collected will be a resource for investigators seeking to close the gap of health disparities among African American older adults.

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 #:** 23A16

Principal Investigator: Rosie Curiel Cid, PsyD

Organization: University of Miami

Summary: A critical gap in Alzheimer's disease (AD) and Alzheimer's disease related disorders (ADRD) clinical research is the vast under-under-representation of Black/African American (AA) older adults. AD/ADRD is more prevalent in AA individuals relative to white individuals of European ancestry. Early detection is critical for clinical trials aiming to develop optimal therapeutics. Therefore, there is a need to include and deeply phenotype AAs using novel cognitive and biomarker assessments that consider the multiple co-morbidities identified in this population. Study location is one of the most important enrollment barriers for AA older adults. This research proposal leverages the researcher's expertise in home-based assessment to evaluate clinical and neuropsychological status. The research team will provide door-to-door transportation for MRI studies to facilitate and support the engagement of AA older adults. Other novel innovative aspects include: a) the use of a well-validated cognitive semantic interference test that is highly related to biomarkers of AD and which have shown to be effective for use in AA older adults with and without Mild Cognitive Impairment (MCI); b) use of promising blood-based biomarkers (BBM) of AD and neurodegeneration that leverage extremely sensitive single molecule array (SiMoA) technology to detect specific proteins in the plasma; c) comparison of BBM with neurodegenerative changes on MRI using sensitive imaging techniques including extracellular free water; d) examining comorbidities, the research team will obtain sensitive measures of cerebrovascular, metabolic and genetic risk by measuring physical, clinical, blood-based, and neuroimaging variables; e) social determinants of health will also be assessed. This unique deep phenotyping of 100 AA older adults will allow the researchers to gain the critical preliminary data needed to apply for extramural funding to further study and longitudinally follow this invaluable cohort of persons who have a disproportionate risk for ADRD.

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 #:** 23A17

Principal Investigator: Claes Wahlestedt, MD, PhD

Organization: University of Miami

Summary: Alzheimer's Disease (AD) is a neurodegenerative disorder where aging is the biggest risk factor. It has been well described that inhibition of the kinase, mammalian target of rapamycin (mTOR), improves age-related pathologies including AD. However, mTOR exists as

a complex and exerts differential functions depending on its binding partners. Regulatory-associated protein of mTOR (raptor) is a component of mTOR complex 1 (mTORC1) while rapamycin-insensitive companion of mTOR (rictor) is a component of mTORC2. Suppression of mTORC1 has yielded positive outcomes for AD-related measures (decreased amyloid beta and tau deposition, improved brain insulin sensitivity, and improved cognitive function) and upregulating mTORC2 via rictor also resulted in positive outcomes in AD models, suggesting an increased ratio of mTORC2 to mTORC1 is desirable for AD. Commonly used small molecule inhibitors of mTOR do not discriminate between mTORC1 and mTORC2, as mTOR is a component of both. Furthermore, small molecules targeting unique binding partners of either complex lack specificity and tend to have pleiotropic effects. The project proposes to inhibit mTORC1 and upregulate mTORC2 using ribonucleic acid (RNA) therapeutics targeting the sense transcript of raptor and the natural antisense transcript (NAT) of rictor for degradation. Research staff hypothesize that increasing the mTORC2/1 ratio with highly selective RNA therapeutics which bind it's targets based on sequence complementarity will decrease both amyloid beta accumulation and tau phosphorylation (hallmarks of AD), as well as improve other AD-related cellular functions in a cell type specific manner, with minimal off-target effects. Staff plan on targeting Raptor and the NAT for Rictor in vitro and in vivo. The preliminary data indicate that targeting the NAT of a target with RNA therapeutics results in increased upregulation of the target. Staff have successfully identified the sequences needed to efficiently target both Rictor and Raptor. The overall therapeutic approach is built on technologies developed in the Wahlestedt lab over the past two decades. Moreover, some of the specifics of the present application are covered in a pending patent application from the University of Miami. The team has successfully used RNA therapeutic techniques in the past and participated in projects that are now at the clinical stage. Notably, the team has published unique work relating to RNA mediated gene upregulation (e.g., Science 2005: Nature Rev Drug Discovery, in press 2022). Additionally, the team has successfully published on pre-clinical drug discovery in AD mouse models and human cells. Increasing the expression of a target gene has traditionally been very difficult. It is biochemically easier indeed to block the activity of a target than to increase it. Work has shown that by targeting NATs, the research team can successfully increase the expression of a target gene. To date, no person has successfully targeted the NAT of Rictor to mitigate AD pathology, while also targeting the mTOR pathway (one of the most validated aging pathways). Data from the proposed work has the potential to yield a novel therapeutic strategy for AD and to promote healthy aging.

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

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

18. **Grant #:** 23A18

Principal Investigator: Hongdao Meng, MD, MPH, PhD

Organization: University of South Florida

Summary: Alzheimer's Disease and related dementias (ADRD) affect more than 42% (400,000) of residents in assisted living (AL) communities. Up to 90% of persons with ADRD experience neuropsychiatric symptoms (NPS, e.g., agitation, anxiety, and apathy) during the disease progression. NPS are associated with functional decline, poor quality of life, and contributes to resistance to care in AL. Current evidence suggests that participating in music activities improves mood and reduces NPS among persons living with dementia (PLWD). However, there is a lack of evidence-based music interventions that can be disseminated widely in memory care units in ALs. The lack of such interventions remains a key barrier to improving the quality of life for the growing PLWD population. With the support from the Ed and Ethel Moore Alzheimer's Disease Research Program's Pilot Program (Grant 9AZ28; principle investigator Meng), the University of South Florida (USF) team demonstrated preliminary feasibility and acceptability of the USF Group Music Intervention (USF-GMI) in two memory care communities. The USF-GMI program consisted of 12 group sessions of music video for reminiscence delivered over four weeks (50-minute per session, three sessions per week). The proposed research project will build on the early success of the pilot study by refining the USF-GMI program, developing staff-training program, and pilot test the resulting program in a cluster-randomized trial (CRT). The specific aims of the proposed pilot CRT are to: conduct qualitative interviews with key stakeholders (AL administrators and activity directors, and dementia care training experts) in three ALs to obtain their assessment of the USF-GMI program and confirm their priorities, needs, constraints, and other determinants of implementation to adapt the program for the current trial; refine the protocol and produce a customized training program based on the standard operating procedures and training manuals developed in the pilot study for the training of memory care staff; and pilot test the resulting refined intervention program as implemented by AL staff in reducing agitation among residents with ADRD. The researchers will enroll six AL communities with memory care units in the Tampa Bay area and conduct a cluster-randomized trial. ALs will be randomized into USF-GMI intervention or usual care groups. The primary outcome variable will be neuropsychiatric symptoms (NPS), as measured by the Cohen-Mansfield Agitation Inventory (CMAI). The secondary outcome will be care staff strain and psychotropic medication use. Qualitative methods will also be used to gain an indepth understanding of the personal (e.g. motivation, perceived benefits), structural (e.g. space, equipment, and staffing), and program (protocol, training, and technical support) factors that will aid in the interpretation of the trial findings and the scaling of the intervention in a future efficacy trial.

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 2022-2023 Active Grant Details

Funded Fiscal Year 2021-2022

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
22A01	Florida Atlantic University	Randy Blakely, PhD	349,819.00	3/31/2024	Yes	No	No
22A03	Florida State University	Robert Tomko Jr., PhD	$100,000.00	3/31/2024	No	No	Yes
22A04	Mayo Clinic Jacksonville	Yang You, PhD	$100,000.00	3/31/2024	No	No	Yes
22A07	Mayo Clinic Jacksonville	Fabienne Fiesel, PhD	350,000.00	3/31/2026	No	No	No
22A08	Mayo Clinic Jacksonville	Yasuteru Inoue, MD, PhD	$100,000.00	3/31/2024	No	No	Yes
22A09	Mayo Clinic Jacksonville	Nilufer Ertekin-Taner, MD, PhD	350,000.00	3/31/2024	No	No	No
22A10	University of Central Florida	Nichole Lighthall, PhD	$742,833.00	3/31/2026	No	Yes	Yes
22A11	University of Florida	Jeremy Grant, PhD	$99,569.00	6/30/2024	No	Yes	No
22A12	University of Florida	Adam Barnas, PhD	$100,000.00	3/31/2024	No	Yes	Yes
22A13	University of Florida	Jada Lewis, PhD	$350,000.00	3/31/2025	No	No	No
22A14	University of Miami	Claes Wahlestedt, MD, PhD	$349,981.00	3/31/2024	No	No	No
22A15	University of Miami	Karen Nuytemans, PhD	$350,000.00	3/31/2024	No	No	No
22A17	University of South Florida	Hariom Yadav, PhD	$743,661.00	3/31/2026	No	Yes	Yes

1. **Grant #:** 22A01

Principal Investigator: Randy Blakely, PhD

Organization: Florida Atlantic University

Summary: 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, the research team discovered an unstudied gene in the small soil worm C. elegans, termed swip-10, finding that its function in non-neuronal (glial) cells supports the health and signaling of nearby neurons in vivo. Current work with the worm model supports a "two-hit model" for the contribution of swip-10 to neuronal health, whereby mutation of the gene diminishes levels a specific copper ion (Cu(I)), leading to altered mitochondrial metabolism and oxidative stress, changes that can cause neurodegeneration. Following this discovery, the Blakely lab identified the gene metallo-beta-lactamase Doman Containing Protein 1 (MBLAC1) as the closest mouse and human version of swip-10. Recently, human genetic studies identified MBLAC1 as a risk factor for AD with co-morbid cardiovascular disease (AD-CVD). Expression of MBLAC1 was found to be reduced in postmortem AD-CDV brain, compared to healthy, age-matched controls. The research team hypothesizes that the contribution of MBLAC1 with comorbid heart disease may reflect the intense energy demands characteristic of both brain and heart. Importantly, this group recently demonstrated that MBLAC1 protein is the major, if not sole target in the mouse brain for the Food and Drug Administration (FDA) approved drug, ceftriaxone (CEF), a molecule reported to have neuroprotective activity, including in AD mouse and rat models. This proposal uses an iterative approach, utilizing both worm (swip-10 mutants) and mouse (MBLAC1 gene knockout (KO)) models, to more deeply characterize the biological mechanisms engaged by chemically

targeting MBLAC1, studies that this team believes may lead to much needed therapeutic options for AD and its comorbidities. Generated GMC101 (worms expressing Aβ 1-42 which forms amyloid plaques) and used confocal imaging to demonstrate that the presence of a loss of function mutation in swip-10 greatly exaggerates the accumulation and size of Aβ positive plaques. Began testing an analog of CEF in worms. Unlike CEF, this beta-lactam compound does not have antibiotic action, and since worms grow on bacterial plates, this molecule may now allow us to examine pharmacological manipulation of swip-10, efforts that can help us establish a new platform for AD drug development. Generated 30 frozen lines of neonatal astrocytes from MBLAC1 KO mice and their wildtype (WT) littermates. Each line derives from one animal and has been genotyped for sex and the MBLAC1 KO. These lines are now being analyzed for changes in Cu(I) levels and cell energy production and oxidative stress. Collected serum, peripheral tissues from 19 10-12 week old Mblac1 KO mice and WT littermates of both sexes to evaluate changes in genes that reflect changes in peripheral metabolism, particularly in liver as this organ is a major regulator of systemic Cu(I) and where disruptions ultimately are known to lead to neurodegeneration. Initiated expression studies of candidate genes in astrocyte lines, focusing on genes responsive to mitochondrial dysfunction, oxidative stress and Cu(I) homeostasis. This research group updated a patent application that describes the discovery that swip-10/MBLAC1 participate in a Cu+ dependent pathway that leads to changes in cell metabolism, mitochondrial function and oxidative stress than explain the increase in risk shown in Genome-wide association studies (GWAS) studies for Alzheimer's disease with cardiovascular comorbidity, and that describes the use of swip-10/MBLAC1 mutants to identify new molecules and treatments related to Cu+ dyshomeostasis including neurodegenerative disease.

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

Collaborations: The team is collaborating with Dr. Christopher Chang at the California Institute of Technology who is supplying the project with a fluorescent probe specific for reduced copper (Cu+). Dr. Chang is also providing mass spectrometry analyses of copper levels in whole worms and mouse tissues and fluids. No funds are derived from the project and no students are involved in Dr. Chang's efforts. Two Blakely lab graduate students (Peter Rodriguez and Jacob LaMar are supported by the project. Both students are involved in the collaboration with Dr. Chang. The lab is collaborating with Dr. Gary Miller at Columbia University who is analyzing the C. elegans metabolome in WT and swip-10 mutant worms. No funds are derived from the project. One Blakely lab graduate student (Peter Rodriguez) is supported by the project and directly involved in the collaboration.

Journals: None at the time of reporting.

Patents: Blakely R, inventor; Florida Atlantic University, assignee. COMPOSITIONS AND METHODS TARGETING SWIP-10 AND MBLAC1 FOR THE THERAPEUTIC MODULATION OF COPPER DYS HOMEOSTASIS, U.S. Provisional Application Serial No. 63/376,993, filed September 23, 2022. Pending.

2. **Grant #:** 22A03

Principal Investigator: Robert Tomko Jr., PhD

Organization: Florida State University

Summary: The goal of the work funded under this award is to engineer biological "nanomachines" that selectively cut up two toxic proteins that help drive Alzheimer's disease (AD): tau and amyloid beta (Aβ). A second goal is to test whether introduction of the most promising nanomachines into neurons can protect them from the toxicity of tau and Aβ. If successful, these nanomachines will serve as prototypes for a new form of biological therapy (or prophylaxis) for AD. The research team has built upon their successful demonstration that protein-specific nanomachines can, in fact, be developed by extending this approach to tau and Aβ. The research eam proposed and has been using "lures" for tau and Aβ that were curated from the available AD scientific literature. However, in the research team's hands, these "lures" do not seem to "catch" tau or Aβ (or potentially, the specific forms of tau and Aβ the research team is targeting). The exact reason for this is unknown, but it has complicated testing of the overarching hypothesis. In light of this, the research team is now producing "tagged" forms of tau and Aβ that can be captured by a different set of "lures." Although the results of these experiments may not be directly useful as a therapeutic, they will demonstrate whether or not the approach can be used in living cells to clear out toxic forms of tau or Aβ as originally proposed. The approach could then be furthered by the development of more effective "lures" for tau and Aβ, which could be grafted onto the nanomachine to "catch" these proteins as originally intended. In a second line of work, the research team is exploring whether an endogenous nanomachine called the proteasome can be hijacked to preferentially clear toxic forms of tau and Aβ. Toward this goal, the research team has created an inducible targeting adaptor that is readily produced in human cells and is currently in testing for recruitment of target proteins for degradation via this endogenous cellular machine. If successful with the model protein the research team has used for development of the approach, then it will be extended to tagged forms of tau and Aβ to demonstrate utility in human cells.

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

Collaborations: None at the time of reporting.

Journals: Betancourt D, Lawal T, Tomko RJ. Wiggle and shake: Managing and exploiting conformational dynamics during proteasome biogenesis. *Biomolecules*. 2023;13(8):1223. doi:10.3390/biom13081223.

Nemec AA, Tomko RJ Jr. An unstructured proteasome inhibitor comes into focus. *J Biol Chem*. 2023;299(9):105145. doi:10.1016/j.jbc.2023.105145.

Patents: None at the time of reporting.

3. **Grant #:** 22A04

Principal Investigator: Yang You, PhD

Organization: Mayo Clinic Jacksonville

Summary: Research staff requested and received two new human stem cell lines derived from Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) patients burdening with P301L tau mutations. The goal was to use these two lines as resources for generating tau organoids instead of exogenously infecting them with adeno-associated viral vector (AAV) viruses, which would provide a more solid and convincing association with disease models. Research staff successfully characterized these two mutant lines and generated them into three dimensional (3D) organoids. Next, research staff added sonicated tau fibrils extracted from Alzheimer's disease patient brain tissue to both normal and tau mutant organoids to facilitate tau pathology in vitro culture. The research staff evaluated the tau pathology in normal and tau mutant organoids after administration of sonicated tau fibrils using immunostaining with hyper-phosphorylated tau antibody AT8, misfolded tau antibody MC1, and tau tangles (FSB and Thioflavin S). However, no significant difference in AT8 and MC1 staining was observed between wildtype (WT) and tau mutant organoids, regardless of tau fibril treatment. Project leader hypothesized that the seeding capability or concentration of sonicated tau fibrils extracted from these AD samples may not be sufficient to induce tau disease progression. Therefore, commercial preformed tau-441 (2N4R) tau fibrils (PFFs) from rPeptide as used, which have been validated to be capable of inducing tau pathology in other studies. The 2ug/uL 2N4R tau fibrils were added to the three-month-old organoids and harvested them after four weeks of incubation. Research staff assessed tau pathology in normal and tau mutant organoids using the same immunostaining methods. These results showed increased AT8 staining in P301L organoids compared to WT organoids in the basal level (Sham group). The administration of tau PFFs in organoids for four weeks resulted in significantly upregulated AT8 levels in the P301L group, rather than the WT group. This suggests the potential recapitulation of Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) disease using the in vitro 3D organoid model. Additionally, research staff observed an increase in total Tau levels in P301L organoids after treating with tau fibrils, likely due to the elevated tau uptake in P301L organoids compared to WT organoids. To gain a better understanding of transcriptomics changes in disease-associated 3D cell models, project leader plans to perform single-cell ribonucleic acid sequencing (scRNA-seq) on the WT and P301L Tau organoids. Research staff have established the protocols for generating single-cell suspension, cell fixation, barcoding, and library preparation from organoid samples using the Parse single-cell RNAseq Mini kit. Furthermore, project leader has collaborated with the Bioengineering team at Mayo to 3D print the assembloid module to fuse tau organoids with other organoids for tau propagation studies. Three organoids were placed on one side of the module and fused them for ten days, demonstrating the feasibility of generating assembloids for studying tau propagation using bioengineered modules. These progresses will lead to the development of the in vitro 3D organoid model for studying tauopathies, which will be a novel platform for high-throughput drug screening to find potential therapeutic targets for neurodegenerative diseases.

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

Collaborations: None at the time of reporting.

Journals: You Y, Zhang Z, Sultana N, et al. ATP1A3 as a target for isolating neuron-specific extracellular vesicles from human brain and biofluids. *Science Advances*. 2023;9(37). doi:10.1126/sciadv.adi3647.

Zhang Z, Yu K, You Y, et al. Comprehensive characterization of human brain-derived extracellular vesicles using multiple isolation methods: Implications for diagnostic and therapeutic applications. *J Extracell Vesicles*. 2023;12(8):e12358. doi:10.1002/jev2.12358.

Patents: None at the time of reporting.

4. **Grant #:** 22A07

Principal Investigator: Fabienne Fiesel, PhD

Organization: Mayo Clinic Jacksonville

Summary: Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting more than five individuals in the United States (US) with close to 500,000 in Florida alone. Clinically, AD is characterized by severe cognitive, behavioral, and motor impairments resulting from progressive synaptic dysfunctions and neuronal loss. Neuropathologically, AD is defined by the formation of insoluble protein aggregates including extracellular amyloid-beta (Aβ) plaques and intracellular tau tangles. However, the molecular mechanism(s) 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. UFM1 has further been implicated in several key cellular processes that are known to be affected in AD, such as the deoxyribonucleic acid (DNA) damage response, the endoplasmic reticulum (ER) stress response and autophagy. In the past year, the research team has developed novel biological assays to analyze components of the UFM1 pathway and applied these to a comprehensive analysis of human post-mortem brain samples. The cohort consisted of cortex samples from AD (n=70) and controls (n=40). The team found that UFM1 is abnormally upregulated in AD while the cognate protease UFM1-specific peptidase 2 (UFSP2) is downregulated in the insoluble fraction. These findings indicated that the UFM1 pathway is altered in AD. This might also indicate that the UFM1 might play a role for the pathogenesis of AD and so it might affect the health outcomes of Floridians with AD. The research team is currently preparing a manuscript for the public dissemination of the research findings. More research is now needed to understand if this pathway can be targeted as a potential therapeutic avenue to improve the onset, prognosis, or disease symptoms of patients. The research team has further worked to generate new research tools and cell models to better understand the role of UFM1 for the nervous system in general. Findings from these novel tools and models will be important to further establish the molecular mechanisms of how the UFM1 pathway is connected to AD and how manipulating it might change the outcome of disease.

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

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

5. **Grant #:** 22A08

Principal Investigator: Yasuteru Inoue, MD, PhD

Organization: Mayo Clinic Jacksonville

Summary: The proposed research focused on investigating the influence of apolipoprotein (APOE) genotypes on cerebrovascular integrity, utilizing human brain samples and induced pluripotent stem cel (iPSC)-derived cerebrovascular cells, including mural cells and endothelial cells. The study first aimed to define the APOE genotype-related effects on cerebrovasculatures using human brain samples. The initial research phase involved optimizing the method for isolating vascular components from brain tissues, resulting in improved purities. Specific cerebrovascular markers, smooth muscle cells (α-SMA) and cluster of differentiation (CD31) for identifying smooth muscle cells and endothelial cells, were used for confirmation. Western blot analysis and immunohistochemical analyses clearly demonstrated that vascular fractions displayed positive immunostaining for α-SMA and CD31, while the neuronal fraction showed negative immunostaining for α-SMA and CD31, and instead, exhibited positivity for neuronal nuclear protein (NeuN), indicating the dominance of neuronal components. A total of 91 brain tissue samples with various APOE genotypes (APOE 2/3, 2/4, 3/3, 3/4, 4/4) were obtained from the Mayo Clinic Brain Bank, and the processing of the vascular-enriched components was completed. The next steps will involve quantifying levels of amyloid beta (Aβ)40, Aβ42, and various vascular extracellular matrix (ECM) components using enzyme-linked immunosorbent assay (ELISA), as well as performing lipidomics and proteomics. The preliminary ELISA analyses also explored Aβ levels in the vascular fractions and identified higher Aβ40 and Aβ42 levels in individuals with a cerebral amyloid angiopathy (CAA) score of 2 (severe cases) compared to those with a score of 0 (non-CAA cases). Additionally, the Aβ40/42 ratios were elevated in the CAA score 2 group compared to CAA score 0. Preliminary proteomic analyses involving 18 samples demonstrated differences in protein expression between various APOE genotypes and CAA status. In moderate to severe CAA group, elevated expression of microtubule associated protein tau (MAPT) was observed in the APOE4/4 group, while fibromodulin (FMOD) expression was higher in the APOE 3/4 group. In the non-CAA group, glycogenin 1 (GYG1) exhibited increased expression in the APOE 3/3 group. Weighted gene co-expression network analysis (WGCNA) highlighted a significant reduction in the proteoglycan-related protein module in CAA, indicating potential damage to vascular components. Future steps in ELISA and proteomics include expanding the sample size to 91 samples and conducting integrated analyses. Researchers then aimed to investigate the effects of APOE genotypes on cerebrovascular functions using an iPSC-derived cerebrovascular model. The study successfully differentiated human iPSCs with different APOE genotypes into brain microvascular endothelial cells and vascular mural cells. The integrity of the endothelial cells was assessed through trans-endothelial electrical resistance (TEER) measurements, indicating robust blood-brain barrier (BBB) formation. In summary, the study successfully isolated vascular fractions from human brain samples and developed an iPSC-derived

cerebrovascular model. It aimed to explore the influence of APOE genotypes on cerebrovascular components and functions, uncovering significant differences in protein expression associated with APOE genotypes and CAA status. The research will provide deep insights into the cerebrovascular system upon completion of this study.

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

Collaborations: None at the time of reporting.

Journals: Inoue Y, Shue F, Bu G, Kanekiyo T. Pathophysiology and probable etiology of cerebral small vessel disease in vascular dementia and Alzheimer's disease. *Mol Neurodegener*. 2023;18(1):46. Published 2023 Jul 11. doi:10.1186/s13024-023-00640-5.

Inoue Y, Bamkole M, Kanekiyo T. Hepatic soluble epoxide hydrolase: A promising target for unveiling the liver-brain axis in Alzheimer's disease. *Neuron*. 2023;111(18):2775-2777. doi:10.1016/j.neuron.2023.08.019.

Patents: None at the time of reporting.

6. **Grant #:** 22A09

Principal Investigator: Nilufer Ertekin-Taner, MD, PhD

Organization: Mayo Clinic Jacksonville

Summary: Cerebral amyloid angiopathy (CAA), a common neuropathological finding in the brains of Alzheimer's Disease (AD) patients, is characterized by an accumulation of amyloid beta (Aβ) in the brain cerebrovasculature. This impacts blood vessel integrity leading to brain hemorrhages and accelerated cognitive decline. Established risk factors for CAA include AD neuropathology (Aβ plaques and tau neurofibrillary tangles), male sex and the apolipoprotein E (APOEε)4 allele. More recently, the research team identified a splice variant within long intergenic non-protein coding ribonucleaic acid (LINC-PINT) that decreases risk for CAA in AD cases that do not carry APOEε4. The central hypothesis is that additional genetic risk factors for CAA remain to be identified and that some of these may have different effects in the context of the established risk factors. However, identifying these will require larger study cohorts. The state of Florida has an aged population; age is a major risk factor for AD and is the fifth leading cause of death in individuals over 65 (Alzheimer's disease facts and figures 2020, Alzheimer's Association). CAA plays a key role in AD pathogenesis, leading to brain hemorrhages and accelerated cognitive decline. Distinguishing patients at risk of brain hemorrhages is especially important given that a significant side-effect of the now Food and Drug Administraion (FDA)-approved anti-Aß therapy aducanumab is brain hemorrhages. However, there are currently no low-cost peripheral biomarkers for CAA.

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 #:** 22A10

Principal Investigator: Nichole Lighthall, PhD

Organization: University of Central Florida

Summary: 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 targets a 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 which is home to over 9% of US Alzheimer's 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, this consortium of researchers at the University of Central Florida (UCF), University of Florida (UF), and University of Miami (UM), have begun to yield basic and applied research findings. The researchers began to determine age group differences in vulnerabilities to exploitation and deception across adulthood, and determine additional risk factors for vulnerabilities to exploitation and deception among older adults. The project has also yielded benefits to the health and wellbeing of Florida older adults and their families. These additional benefits include the provision of education to older adults and community stakeholders who serve older adults about age-related vulnerabilities to fraud and scams, and the development of partnerships with legal entities specializing in elder fraud, media liaisons, healthcare providers, senior residential living communities, and life-long learning groups that will provide a foundation to promote culturally-sensitive education and interventions against elder fraud and misinformation/disinformation campaigns that target older adults. The research team successfully launched data collection for the longitudinal investigation into the psychological and neural mechanisms of deception detection in aging and AD. The team also disseminated research from the foundational work that led to this grant. This work has already identified specific cognitive, affective, and social predictors of deception susceptibility. The project team has examined these factors in a range of contexts, including novel digital contexts that are increasing utilized to deceive and defraud older adults. Finally, research project staff have consistently engaged with the community though education and partnership building to reduce deception and exploitation of older adults. A highlight in this domain includes the team's plan to incorporate an educational intervention to detect and reduce scams susceptibility in older adults at the conclusion of the study. This intervention will help us to meet the consortium object of providing access to 'accountable science', through educational offerings that translate Summary data and concepts into common language to equip Floridians with the skills needed to identify, report, and avoid exploitation of vulnerable elders.

Follow-on Funding: Federal Agency/Institute: University of Central Florida, College of Sciences; ; Principal Investigator: Lighthall N; Grant Term: 2/3/2023 – 2/2/2024; Grant Category:

Colelge of Sciences SEED grant; Submission Date: 11/30/2022; Total Funds Requested: $34,740.00; Total Funds Awarded: $34,740.00; Status: Funded.

Federal Agency/Institute: National Institute of Health; Principal Investigator: Lighthall N, Ebner; Grant Term: 8/1/2022 – 4/30/2027; Grant Category: R01 Diversity Supplement; Submission Date: 5/16/2022; Total Funds Requested: $330,162.00; Total Funds Awarded: $328,639.00. Status: Funded.

Federal Agency/Institute: National Institute of Health; Principal Investigator: Lighthall N; Grant Term: 12/1/2023 – 11/30/2025; Grant Category: R01 Diversity Supplement; Submission Date: 9/29/2023; Total Funds Requested: $142, 071.00; Status: Pending.

Federal Agency/Institute: Florida Department of Health Ed and Ethel Moore Alzheimer's Disease Research Program; Principal Investigator: Ebner; Grant Term: 7/1/2024 – 6/30/2027; Grant Category: Standard Grant; Submission Date: 8/15/2023; Total Funds Requested: $ 349,993.00; Status: Pending.

Federal Agency/Institute: Scientific Research Network on Decision Neuroscience & Aging Diversity Research Award (award under NIH funded network, grant: R24-AG076847); Principal Investigator: Lighthall N; Grant Term: 5/15/2023 - 9/01/2023; Grant Category: Undergraduate Research Fellowship; Submission Date: 3/1/2023; Total Funds Requested: $3,400.00; Total Fundas Awarded: $3,500.00; Status: Funded.

Federal Agency/Institute: University of Central Florida Office of Udnergraduate Research; Principal Investigator: Lighthall N; Grant Term: 5/19/2023 – 7/21/2023; Grant Category: Undergraduate Research Fellowship ($2,000 for each of 5 undergraduate students); Submission Date: 3/10/2023; Total Funds Requested: $10,000.00; Total Funds Awarded: $10,000.00. Status: Funded.

Collaborations: This is a consortium grant involving three Florida universities (University of Central Florida (UCF), University of Florida (UF), and University of Miami (UM)). Implicit in this project is the strong cross-institutional collaboration. Currently under this three-institution project, research training and collaboration has been established for four postdocs, two research scientists, four post-bac students, one Masters level clinical research coordinator, and nine undergraduate students across UCF, UF, and UM sites. Additionally, this year, the consortium consulted with a group at the University of South Florida (USF) regarding this project's approach to recruitment, retainment, and community engagement with diverse older adults in Florida. Associate Dean of Clinical Affairs; Project Director, Workgroup Enhancing Community Advocacy & Research Engagement (WE-CARE) for consultation on strategies for recruiting and retainment older adults from minority communities, including older adults with mild cognitive impairment. As a result of this relationship, this project's lead principal investigator (PI) (Dr. Lighthall) invited the director of WE-CARE (Dr. Angela Hill, USF) to give a talk at a conference for the Scientific Research Network on Decision Neuroscience & Aging. Dr. Hill gave a presentation on "Using a community engagement model to enhance research recruitment and retention." No student trainees from USF are involved in this collaboration at this point, but a number of junior researchers attended the conference (including students from Florida institutions), and benefitted from Dr. Hill's talk. Members of this research team gave three talks at the 2023 meeting of the Florida Consortium on the Neurobiology of Cognition (FCNC) in Jupiter, FL describing research supported by this project. As described by FCNC:

"Across universities and institutes in Florida researchers are utilizing cutting edge techniques to understand how cognition is supported by the brain. The FCNC aims to promote the exchange of ideas and expertise, and foster collaborations throughout the state of Florida. The goal is to discover the fundamental brain mechanisms of cognition – transforming education, technology, and ultimately brain health across the life-span. Every year in the spring researchers come together to share research at the FCNC Annual Meeting. Faculty, post-docs, and graduate students have the opportunity to present their work. The meeting is kicked off by a distinguished keynote lecture." While no formal collaborations developed from this meeting, the team disseminated work from this project to a large group of Florida researchers from faculty to the undergraduate level. Participating institutions that are not already involved in this project included Florida State University, Florida Atlantic University, Florida International University, and Max Planck Florida. The UF site made a connection with faculty at the School of Psychology and School of Cybersecurity at Georgia Tech, Atlanta for collaborative purposes. No students from Georgia Tech are involved in this collaboration at this point. In addition to collaboration with postsecondary education institutions, over this year, research staff have been in communication with Shannon Miller (Miller Elder Law Firm, Gainesville), Dr. Janet Coats (University of Florida Consortium on Trust in Media and Technology), Dr. Damon Woodard (Florida Institute on National Security), UCF Learning Institute for Elders, as well as with cybersecurity experts at the Institute on Human Machine Cognition in Ocala on critical needs in the field for the assessment battery developed in this grant and knowledge translation. Research staff also developed a relationship with the UCF College of Medicine Director of Clinical and Aerospace Health Research (Dr. Amoy Fraser) to discuss methods for recruiting older adults with and without cognitive impairments using their existing infrastructure for research facilitation.

Journals: Doheny MM, Lighthall NR. Social Cognitive Neuroscience in the Digital age. *Front Hum Neurosci*. 2023;17. doi:10.3389/fnhum.2023.1168788.

Patents: None at the time of reporting.

8. **Grant #:** 22A11

Principal Investigator: Jeremy Grant, PhD

Organization: University of Florida

Summary: 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 Alzheimer's Disease (AD). Fifty-five percent of older adults in the United States (US) are estimated to have MeSy, and this estimate is expected to increase in line with the country's increasingly aging population. Physical exercise and proper medication intake are the frontline treatments for MeSy, but many individuals fail to maintain healthy lifestyle behaviors over time. This fellowship grant has allowed the principle investigator (PI) to receive advanced training in clinical neuropsychology and study factors that predict exercise adherence among older adults with MeSy. Specifically, the study examined individual-level predictors of exercise adherence (age, education level, depression, and cardiovascular disease burden) as well as neighborhood disadvantage as contextual-level predictor of exercise

adherence. Since the previous legislative report, the PI has trained research staff to administer the standardized neuropsychological battery of the National Alzheimer's Coordinating Center (NACC) and other neuropsychological measures via videoconference (Zoom). The PI also coordinated several community outreach events to facilitate participant recruitment for the study. Events have included presenting health seminars at four churches in North Central Florida, entitled Steps to Brain Health: How to Prevent Alzheimer's Disease & Dementia, attending two health fairs, and hosting a film screening and discussion at a community center for a documentary on Alzheimer's disease, entitled Keys Bags Names Words. The PI led data collection efforts for the study and 61 older adults underwent neuropsychological evaluation to examine their cognitive strengths and weaknesses. Subsequently these patients recorded their medication intake and physical exercise over an eight-week period, while also a wrist-worn altigraph device recorded data. Summarys have been submitted for two poster presentations, one for the 2023 Annual Meeting of the National Academy of Neuropsychology and one for 2024 Annual Meeting of the International Neuropsychological Society The PI has engaged in research projects involving secondary data analysis of large neuropsychological databases to examine a novel battery approach for differentiating between normal cognitive aging, mild cognitive impairment, and dementia. PI presented two poster presentations at the Annual Meeting of the International Neuropsychological Society (INS) in February 2023 and one at the Annual Convention of the American Psychological Association (APA) in August 2023. The latter was awarded Best Research Summary by an Early-Career Professional by American Psychological Association (APA) Division 40 (Clinical Neuropsychology). The PI has engaged in advanced clinical training in the Department of Clinical & Health Psychology at the University of Florida and conducted two to four supervised neuropsychological assessments per week, assessing patients with Alzheimer's disease and related disorders - Participated in weekly clinical case conferences with the 1Florida Alzheimer;s Disease Research Center (1FL ADRC).

Follow-on Funding: Grant Title: Establishing Quick-Reference Criteria for Identifying Multivariate Cognitive Change in Ethnically Diverse Older Adults; Federal Agency/Institute: University of Wisconsin; Principal Investigator: Grant J; Grant Term: 10/1/2023 – 07/31/2023; Submisison Date: 6/21/2023; Grant Category: Alzheimer's Disease Neuroimaging Initiative (ADNI) Health Equite Scholars Program; Total Funds Requested: $70,000.00; Total Funds Awarded: $70,000.00. Status: Funded.

Grant Title: Investigating Neighborhood Context, Cognition, and Biomarkers of Alzheimer's Disease in Underserved Populations; Federal Agency/Institute: Florida Department of Health,; Principal Investigator: Grant J; Grant Term: 4/1/2023 – 6/30/2027; Submisison Date: 8/15/2023; Grant Category: Ed and Ethel Moore Alzheimer's Disease Research Program; Total Funds Requested: $95,555.80; Total Funds Awarded: $95,556.00; Status: Funded.

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

9. **Grant #:** 22A12

Principal Investigator: Adam Barnas, PhD

Organization: University of Florida

Summary: Spatial navigation is an essential task, and it is common for spatial navigation abilities to degrade during normal aging, with extreme deficits being prevalent symptoms of Alzheimer's Disease (AD). Losing the ability to navigate results in limited mobility, safety concerns, decreased independence, and impaired quality of life for those directly and indirectly living with AD. Deficits in spatial navigation may be exacerbated by deficits in re-orienting visual attention to relevant objects and locations that help people navigate successfully in their environment. Cues like street signs support spatial navigation behavior, but people need to find them, a task requiring visual attention. Whereas AD patients show general deficits attentional functioning, individuals with Mild Cognitive Impairment (MCI) show selective impairments deficits in attentional functioning. Thus, preserving spatial navigation function in aging and age-associated neurodegenerative disease depends upon a thorough understanding of the behavioral and neural underpinnings of attentional function and dysfunction. Measuring visual attention performance and changes to the attentional network in the brains of individuals with MCI and comparing them to healthy older adults will aid in diagnosing and tracking the progression of AD by identifying novel behavioral and neural markers of disease-related dysfunction. Together, these efforts provide the foundation for theoretically motivated and empirically grounded interventions to preserve attentional and spatial navigation abilities and improve quality of life. Understanding the behavioral and neural correlates of attentional re-orienting in MCI/AD allows for alternative diagnostic procedures by establishing the connection between attentional re-orienting deficits and spatial navigation abilities, offering a way to determine who may need clinical help before they get lost. This work is being conducted simultaneously under the parent grant Florida Department of Health (FLDOH) 21A09, which is investigating spatial navigation abilities in young and older adults. Participants who participated in the parent grant project were recruited to this current project. Participants completed two tasks that measure attentional functioning: the double rectangle task to measure attentional selection of locations and objects; and the attention network task to measure attentional mechanisms of alerting, orienting, and distractor filtering. Research staff found that healthy older adults and those with subjective cognitive decline (a frequent clinical precursor state that increases the risk of AD) and a family history of AD show significant impairments in attentional function. For instance, these participants are slower to shift attention between locations and objects and exhibit significant costs in maintaining an alert state and filtering distracting information. Staff also found that attentional function is significantly predictive of spatial navigation success across groups, such that impairments in attention are associated with lower navigation success. However, staff did see that lower navigation success in older adults with spatial direction comprehension (SCD) is significantly correlated with their ability to attend to objects. Thus, attention to objects, and its decline in aging, is crucial to spatial navigation behavior. This work provides a target for future behavioral interventions that aim to enhance attentional selection of objects to increase spatial navigation success in older adults with SCD, providing help to individuals who are at greatest risk of becoming lost.

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

Collaborations: The University of Florida (College of Liberal Arts and Sciences, Department of Psychology; Gainesville, Florida) is involved in this research project, providing institutional resources to support behavioral testing and grant administration. This research project is directly supporting Dr. Barnas.

Journals: Weisberg SM, Chatterjee A. Spatial direction comprehension in images, arrows, and words in two patients with posterior cortical atrophy. *Neuropsychologia*. 2021;151:107697. doi:10.1016/j.neuropsychologia.2020.107697.

Patents: None at the time of reporting.

10. Grant #: 22A13

Principal Investigator: Jada Lewis, PhD

Organization: University of Florida

Summary: Alzheimer's disease and other related dementias (ADRD) are disorders that severely impact the independence, livelihood, daily living, and ultimately, the lives of people in Florida. Furthermore, there are striking impacts on the lives of the friends and family members who provide care for individuals living with these dementias. Financial costs associated with these disorders also tax family and state resources. Florida has a large elderly population and ADRDs are age-associated diseases—as a person ages, the risk of developing one of these dementias grows. It is therefore critical for Florida and the state's aging population that more tools are developed, more research is done, and treatments are sought for these dementias. This grant is focused on characterizing a new mouse model which was built to model multiple aspects of Alzheimer's disease (AD). Although there are other mouse models for these diseases, many of them do not express the human gene in the brain regions needed, are too aggressive, have artefactual loss of nerve cells, or are exceedingly expensive to use. These factors can decrease the use of the mouse model for therapy development for dementia or use in disease-relevant work and can even yield accidentally misleading results. For this current grant, the research team has characterized a line of transgenic mice that express the human gene encoding the tau protein. Tau is a protein that normally binds to the "railroad tracks" of the nerve cells, stabilizing them as crossbars do on a railroad. This normally allows for molecular cargo to be transported back and forth in a nerve cell. The tau protein that the research team inserted in this mouse model contains a mutation (mistake) that is associated with a form of human dementia. Instead of binding to the railroad tracks in the nerve cell, the research team predicted that the tau protein would be less likely to form stable "railroad tracks" and more likely to pile on top of each other into what the field terms a "neurofibrillary tangle". Over the past year, the lab team has identified the best tau mouse model out of the lines that the lab generated and established likely timelines for development and progression of pathology that is similar to the timelines observed in humans with these dementias. The research team has shown that the pathology is remarkably consistent across mice of the same age that are expressing the human tau. The pathology is similar to the pathological changes that occur in human ADRD dementias. The lab has also made good progress in identifying the nature of the shortened lifespan in this model. Over the next year, the lab anticipates that these findings will be published, and the mice

will then be made widely available to any research teams interested in building on knowledge of these dementias and for developing therapies for these diseases.

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 #:** 22A14

Principal Investigator: Claes Wahlestedt, MD, PhD

Organization: University of Miami

Summary: Purpose: Each year, nearly one in three seniors (adults age 65 and older) in the United States (US) 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? Context and progress to date: The research team hypothesizes 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. Last report, the team summarized preliminary results from the research team showing that multiple DNA damage repair enzymes are upregulated in the brain of mice post-exercise. The research team went on to evaluate the effects of exercise in Alzheimer's disease biomarkers in wild type animals to establish a 'normal' baseline for the evaluation of the effect of exercise in Alzheimer's disease models. At baseline, after six months of daily moderate treadmill exercise, exercised mice showed a significant difference in spatial memory compared to sedentary mice. In addition to the animal work, the research team has been investigating more precise DNA damage response mechanisms involved in exercise. Specifically, the team discovered that pathways identified in exercised mice involve selective histone post translational modifications that are implicated in memory formation and control gene expression pathways that are neuroprotective. The results are encouraging and expect a bigger therapeutic window with the Alzheimer's disease mouse models. Consequently, the research project staff is still investigating 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. Impact to Floridians: This proposal addresses goals set forth in both priority eight and nine of the Florida State Health Improvement Plan (SHIP) by considering both the AD-specific neuroprotective mechanisms of exercise as well as the benefits to overall health. Understanding the acute and adaptive exercise-induced DNA damage response in healthy and AD animals will give us a new framework in which to investigate early detection and prevention of AD and its co-morbidities.

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 #:** 22A15

Principal Investigator: Karen Nuytemans, PhD

Organization: University of Miami

Summary: 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 vast majority of genetic research so far has been conducted on individuals of European descent. A recent study in African American cohorts identified 11 novel loci for AD in this population, including a region located between genes RBFOX1 and transmembran protein 114 (TMEM114). Ribonucleic acid binding fox-1 homolog 1 (RBFOX1) was previously reported to influence changes in the cell or brain that are highly relevant to AD, but no direct correlation to AD is known. Therefore, the team wanted to study the function of RBFOX1 in AD context and understand how the identified variants in the recent study in African Americans drive potential changes in RBFOX1. First, researchers created viruses that can shut down or increase expression of RBFOX1 in a constant manner once introduced in the cell type of interest (here; neurons, the cell type in the brain most commonly expressing RBFOX1). Then tested these viruses and the appropriate controls in neuroprogenitor cells (NPCs, cells akin to very immature neurons) of a healthy African American individual to evaluate efficiency of the shutdown or increase of expression and select the best controls. Control viruses most similar to the shutdown and overexpression viruses without affecting RBFOX1 expression were successfully identified. Transduction with the selected viruses was repeated in the NPCs in a larger format and efficiency of the viruses was confirmed. After this quality control, the NPCs were further matured to neurons. A small portion of cells were frozen down at intermediate stages to allow for confirmation of RBFOX1 modulation and future repetition of the experiments. The neuronal cells were kept in culture up to day 55, at which point final samples for evaluation of expression (of RBFOX1 gene and others) and protein levels (AD-relevant amyloid beta (Aβ) fragments and others) were collected and stored. Due to a gap in research staff availability (delay in hiring), the final analyses of expression and proteins will be performed in the next quarter. Second, researchers have designed the necessary ribonucleic (RNA) molecules on either side of the identified variants with high efficiency of driving clustered regualrly interspace short palindromic repeats (CRISPR)- associated protein 9 (Cas9) nuclease activity to allow the

CRISPR/Cas9 system to cut out the variants and surrounding area in the genome (~300bp) of the control cell line. The research team expects the 300bp deletions to result in full removal of genomic elements, such as enhancers, silencers, etc, that are influencing RBFOX1 (or other genes) expression. The CRISPR experiments in the cells of the African American control line will commence in the next quarter. 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 genes (here potentially RBFOX1) and functional 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 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.

13. **Grant #:** 22A17

Principal Investigator: Hariom Yadav, PhD

Organization: University of South Florida

Summary: Florida's elderly population constitutes 23.4% of the state's total population, which is over 4.4 million people aged 60 years and older. This percentage is among the highest in the nation and is expected to exceed 32.5% by 2030. Aging is a significant risk factor for cognitive decline and Alzheimer's disease-related dementia (ADRD). However, predicting who will develop these devastating conditions and initiating care remains challenging, if not impossible. Current early detection methods are often expensive, inaccurate, and invasive. The proposal aims to identify biomarkers in the gut microbiome to develop less burdensome and more accurate markers for mild cognitive impairment (MCI, an early stage of AD) and ADRD. The abnormal gut microbiome produces metabolites that damage gut barrier functions, leading to increased gut permeability ("leaky gut") and inflammation, which in turn exacerbates ADRD pathologyThe project objectives are to establish proof-of-concept that the researchers can differentiate MCI and ADRD patients from their healthy counterparts based on their microbiome signatures, predict the risk and progression of MCI and ADRD; and strengthen the power of microbiome-based differentiation and prediction by combining metabolites and markers of leaky gut and inflammation. The team has made significant progress in this study, with all five sites enrolled in the microbiome in aging of gut and brain (MiaGB) consortium actively involved. Researchers conduct monthly meetings to discuss progress, harmonize protocols, train staff, and collect and analyze samples. The research staff have recruited more than 300 participants and have analyzed over half of the samples for data generation. Additionally, the researchers have published two manuscripts in peer-reviewed journals, presented these findings at conferences and community events, and applied for several National Institutes of Health grants, securing around $420,000 in funding, with additional grants pending. The research staff are also working on expanding the MiaGB consortium to include more than 11 universities nationwide.

The consortium has developed a website (https://miagbstudy.com/) and is working on a dissemination database to make MiaGB data and samples accessible on a national level. The researchers are actively seeking funding from other extramural sources to support multi-omics analyses. This knowledge base will enable us to develop unique, noninvasive, inexpensive, and easy-to-measure microbiome-based biomarkers for predicting MCI and ADRD risk in older adults. Furthermore, these results will provide insights into effective strategies for modulating the abnormal microbiome to prevent or delay ADRD progression. These objectives will be realized through a unique collaboration of experienced research and clinical teams, as well as underrepresented federally funded centers across Florida.

Follow-on Funding: Federal Agency/Institute: National Institutes of Health; Principal Investigator: Jain S; Grant Term: July 2023 – June 2025; Submisison Date: 6/21/2023; Grant Category: NIH R21; Total Funds Requested: $412,344.00; Status: Pending.

In collaboration with Drs. Yadav (PI) and Michal Masternak (UCF site PI) have submitted another ancillary NIH R21 on July 10, 2023 investigating miRNAs using MiaGB samples.

Dr. Yadav has also submitted a R61/R33 grant titled "Microbiome in Aging Biospecimen Biorepository (MABB)" in July 2023, and which due to be reviewed this month. This grant expanded MiaGB consortium to the national level by bringing 6 more universities in the network.

Dr. Yadav is also planning two-three NIH ancillary grants to be submitted early next year in the February/March/April cycle.

Collaborations: The research team has initiated collaboration with the University of North Florida for further studies to involve the students and recruitments at the site. However, no Florida Department of Health (FDOH)-related funding is extended to them. The researchers have also established collaborations with University of Alabama Birmingham, Meharry College of Medicine, University of New Mexico, Montana State University, University of Connecticut and University of Florida, and submitted marker-assisted backcross breeding (MABB) to NIH for funding. The researchers are also in conversation with international sites like in Egypt and India to start sites there to get an international expansion of the MiaGB study.

Journals: Masternak MM, Yadav H. Microbiome in aging of Gut and Brain (MiaGB): paving the ways to understand gut-brain axis in aging. *Aging Pathobiol Ther*. 2022;4(1):1-3. doi:10.31491/apt.2022.03.080.

Powell DS, Oh ES, Lin FR, Deal JA. Hearing Impairment and Cognition in an Aging World. Journal of the Association for Research in Otolaryngology : *JARO*. 2021 Jul;22(4):387-403. doi: 10.1007/s10162-021-00799-y.

Patents: None at the time of reporting.

Appendix B Fiscal Year 2022-2023 Active Grant Details
Funded Fiscal Year 2020-2021

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
21A04	Florida Atlantic University	Qi Zhang, PhD	247,620.00	2/28/2025	Yes	Yes	Yes
21A06	University of Central Florida	Suren Tatulian, PhD	$247,620.00	6/30/2025	No	No	No
21A09	University of Florida	Steven Weisberg, PhD	$247,613.00	2/28/2025	No	Yes	Yes
21A10	University of Florida	Stefan Prokop, MD	$246,991.00	2/28/2025	No	Yes	No
21A21	University of Miami	Grace Zhai, PhD	$247,620.00	2/29/2024	No	No	Yes
21A24	University of South Florida	Laura Blair, PhD	$247,620.00	6/30/2025	No	Yes	Yes

1. **Grant #:** 21A04

Principal Investigator: Qi Zhang, PhD

Organization: Florida Atlantic University

Summary: This project is to investigate if and how brain cholesterol (Chol) dysregulation is the cause of Alzheimer's disease (AD). Studies of genetic mutations associated with rare familial AD (fAD) led to the popular amyloid hypothesis, in which the amyloid peptides are proposed to be the cause of neuronal loss and dementia. However, half of the cognitively normal elderlies have amyloid plaques in their brain. Moreover, therapeutic efforts to reduce amyloid buildup have not been able to reverse or even stop cognitive decline in AD patients. Even for the recently Food and Drug Administration (FDA)-approved anti-amyloid antibodies, they only slow down the decline around 27% in comparison to placebo group, and they are only for the patients with very early phase AD. From millions of patients with the much common sporadic AD, genomic analysis showed that genes linked to cholesterol metabolism and endocytosis are major risk factors. Investigation by research staff showed that fAD mutations in the amyloid precursor protein (APP) impairs Chol balance and triggers neuronal death, suggesting that Chol dysregulation is a more immediate causal factor for AD than amyloid peptides, which may be byproducts. To understand how Chol unbalance can cause neurodegeneration, the research staff will address how neuronal Chol is regulated (especially at nerve terminals), how Chol unbalance affect neuronal function and initiate neuronal death. During the reported funding period, the most significant scientific accomplishments the research staff have made are developing a new fluorescent reporter for Chol, illustrating the turnover of Chol at nerve terminals, delineating the disruption of neuronal Chol by APP deficit and mutations, and observing neuronal breakdown and AD-related pathology caused by APP deficit. These findings provide critical evidence supporting the hypothesis that Chol unbalance can cause AD. The research staff are obtaining more evidence to reveal the mechanism underlying AD origination and are testing ideas to rescue Chol unbalance and to stop neuronal loss. Together, this project will provide a new explanation for the cause of AD and a new strategy for curing or even preventing AD.

Follow-on Funding: Federal Agency/Institute: National Institute of Health; Principal Investigator: Zhang Q; Grant Term: 1/1/2024 – 12/31/2028; Submisison Date: 6/5/2023; Grant Category: R01; Total Funds Requested: $2,399,337.00; Status: Pending.

Collaborations: The research staff 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 the research team to assess changes in APP, secretase, synaptic proteins, and all AD-related gene expression changes using both biochemical and genomic methods.

Journals: Mesa H, Zhang EY, Wang Y, Zhang Q. Human neurons lacking amyloid precursor protein exhibit cholesterol-associated developmental and presynaptic deficits. *J Cell Physiol*. Published online March 26, 2023. doi:10.1002/jcp.30999.

Patents: Zhang Q, inventor; Florida Atlantic University, assignee; Environmentally sensitive lipid analogs; Provisional Patent Application submitted;Case Number: FAU 2022-036; Reference number: 11605-050PV1.

2. **Grant #:** 21A06

Principal Investigator: Suren Tatulian, PhD

Organization: University of Central Florida

Summary: The secondary and tertiary structures of four amyloid beta (Aβ) species Aβ1-42, Aβ1-40, and the pyroglutamylated protein database eXchange beta 3-42 (pEAβ3-42) and pEAβ3-40 have been studied by circular dichroism (CD), fluoerscence, and Fourier transform infrared (FTIR) spectroscopy in the presence and absence of lipid membranes. CD spectra of Aβ1-42 indicated β-sheet structure with and without membranes. Aβ1-40 displayed β-sheet and unordered structures. Spectra of pEAβ3-42 and pEAβ3-40 suggested β-sheet structure without membranes and additional α-helix structure with membranes. Fluorescence studies were conducted using excitation wavelengths (λex) from 210 nm to 275 nm. Aβ1-42 produced tyrosine (Tyr) fluorescence at 307 nm at all λex. Aβ1-40 displayed weaker and blue-shifted fluorescence suggesting that phenylalanine contributes to fluorescence more than in case of Aβ1-42 because Tyr of Aβ1-40 is exposed to and quenched by the buffer. For the extruded samples of Aβ1-40, at λex = 230 nm the emission band was split into peaks around 306 and 340 nm. The red-shifted component of Tyr emission can be rationalized in terms of strong H-bonding of the phenolic hydroxyl (OH) group to a base such as human phenotype ontology 42 (HPO42) and deprotonation. The pEAβ3-42 and pEAβ3-40 peptides generated split spectra in buffer; the presence of membranes partially prevented the splitting suggesting solvent protection by membrane. The lack of splitting in case of Aβ1-42 indicates this peptide forms a more compact, solvent-protected β-sheet structure in the presence or absence of membranes. The importance of these findings is that Tyr fluorescence can be used to determine the degree of solvent accessibility of the peptides. Aβ1-42 is effectively inserted into lipid membranes and is expected to form ion-conducting channels. The other three peptides are more solvent-exposed. FTIR studies identified the effects of the peptides on lipid order in supported membranes. Aβ1-42 increased whereas the other three peptides decrease the lipid order. Membrane channel formation by Aβ1-42, Aβ1-40, pEAβ3-42, and pEAβ3-40 has been studied by voltage clamp experiments. Around five minutes following addition of Aβ1-42, the current reached around 40 pA, featuring stepwise transitions between discrete conductance levels, suggesting that Aβ1-42 inserts into the membrane and forms ion-conducting channels. Membrane conductance induced by pEAβ3-42 involved both stepwise and high frequency burst-like patterns. In addition, events

of sudden jump between different macro conductance levels occurred. Aβ1-40 displayed infrequent burst-like current spikes with less than 50 milliseconds duration that were superimposed on a zero current level. pEAβ3-40 exhibited a combination of step-like and burst-like activities, with a higher frequency and conductance magnitude of burst-like events compared to Aβ1-40 and pEAβ3-42. The burst-like activities of pEAβ3-40 were continuous throughout the recording and showed similar behavior at all applied voltages between +100 and -100 mV. These data reveal distinct structural and membrane channel forming features of the Aβ peptides. Aβ1-42 inserts into membranes and produces single-channel-like currents. Aβ1-40 displays a conformation rich in turn and unordered structures, with little β-sheet, fails to effectively embed in membranes, and produces infrequent bursts of current. pEAβ3-42 and pEAβ3-40 induce large channel-like currents that may contribute to their hypertoxicity.

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

Collaborations: Professor Ratnesh Lal, Dept. of Bioengineering, Mechanical Engineering, Materials Science and Engineering. Abhijith Karkisaval Ganapati, PhD student in Professor Lal's lab. Professor Lal and Abhijith conducted electrophysiological experiments on amyloid beta peptides and recorded ion-conducting channels in lipid membranes. A manuscript containing the structural and channel data has been submitted for publication and currently is under revision .

Journals: None at the time of reporting.

Patents: None at the time of reporting.

3. **Grant #:** 21A09

Principal Investigator: Steven Weisberg, PhD

Organization: University of Florida

Summary: 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. 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). The research team's approach combines behavioral, neural, and genotypic assessment with a novel real-time neurofeedback intervention. The research team proposes three specific aims: determine the behavioral and neural correlates of spatial navigation strategies in healthy older adults and older adults who are at risk for developing Alzheimer's disease, i.e., diagnosed with amnestic mild cognitive impairment (aMCI); 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; and determine whether carriers of a genetic marker, apolipoprotein E4 (ApoE4), which predisposes carriers to develop Alzheimer's disease, are more likely to show navigation deficits or may be more (or less) amenable to rtfMRI interventions. In particular, the research team 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 research team hypothesize that this neural shift and associated behavioral effects are more pronounced in individuals at elevated risk for developing Alzheimer's disease (i.e., ApoE4 allele carriers) and in aMCI. 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 the patient gets lost or wanders.

Follow-on Funding: Grant Title: Novel Behavioral and Neural Markers of Alzheimer's Disease Progression: A Case of Visual Orienting; Federal Agency/Institute: Florida Department of Health; Principal Investigator: Barnas A; Grant Term: 4/1/2022 – 6/30/2024; Submisison Date: 9/10/2021; Grant Category: Ed and Ethel Moore Alzheimer's Disease Research Program; Total Funds Requested: $100,000.00; Total Funds Awarded: $10,000.00; Status: Funded.

Grant Title: Older Adult decision-making and navigation behavior; Federal Agency/Institute: University of Florida; Principal Investigator: Perez E; Grant Term: 1/1/2022 – 3/31/2022; Submisison Date: 10/1/2021; Grant Category: Goldman Spring Scholarship; Total Funds Requested: $6,000.00; Total Funds Awarded: $6,000.00; Status: Funded.

Grant Title: Eliany Perez T32 to support her dissertation research, which will analyze spatial navigation strategy through fMRI, rt-fMRI, and behavioral analyses; Principal Investigator: Marsiske M; Grant Term: 8/31/2023 – 8/30/2025; Submisison Date: 7/2023; Grant Category: T32; Total Funds Requested: 2 years research support for Ms. Perez; Total Funds Awarded: 2 years research support for Ms. Perez; Status: Funded.

Collaborations: None at the time of reporting.

Journals: Weisberg SM, Chatterjee A. Spatial direction comprehension in images, arrows, and words in two patients with posterior cortical atrophy. *Neuropsychologia*. 2021;151:107697. doi:10.1016/j.neuropsychologia.2020.107697.

Weisberg SM, Ebner NC, Seidler RD. Getting LOST: A conceptual framework for supporting and enhancing spatial navigation in aging. *Wiley Interdiscip Rev Cogn Sci*. Published online November 7, 2023. doi:10.1002/wcs.1669.

Patents: None at the time of reporting.

4. **Grant #:** 21A10

Principal Investigator: Stefan Prokop, MD

Organization: University of Florida

Summary: Alzheimer's disease (AD) is the most common cause of dementia, currently affecting more than 580,000 Floridians. It is well 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. The overarching goal of this proposal is to recruit Floridian who 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 second and beginning of the third year 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 the research team to recruit a total of 65 COVID-19 survivors into the brain donation program. All these participants subsequently died, and the research team were able to procure the brains for the UF HBTB. Neuropathological workup has been completed on all 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. The research team have analyzed the local immune response in a subset of these brains and compared the findings with existing data sets of patients who suffered from neurodegenerative diseases but did not have a COVID-19 infection. These analyses revealed elevated inflammation in the brains of COVID-survivors, indicating that the infection had a lasting effect on brain immunity. The research team have also identified a profound impact on pathways related to oligodendrocytes and myelination, both of which appear to be severely downregulated in patients surviving a severe systemic infection. The research team has not detected any differences in the extent of neurodegenerative pathology in COVID-19 survivors compared to cases without a history of COVID-19 infection, but these studies are still ongoing as the research team recruit more and more patients into the brain donation program. Recruitment efforts in the second and early third year of funding have been extremely successful and the research team are 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 the 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: Federal Agency/Institute: Naitonal Institutes of Health/National Institutes on Aging; Principal Investigator: Prokop, Moldawer, Chakrabarty; Grant Term: 8/15/2022-8/31/2027; Submisison Date: 10/2021; Grant Category: R01; Total Funds Requested: $2,200,000.00; Total Funds Awarded: $2,200,000.00; Status: Funded.

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

5. **Grant #:** 21A21

Principal Investigator: Grace Zhai, PhD

Organization: University of Miami

Summary:

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. The researchers 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 preliminary data showing the impact of sleep disruption on protein aggregation. This study will integrate high resolution immunofluorescent and electromicroscopic 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. The 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. In the past year of the grant, have successfully gathered experimental tools and reagents, established the experimental models, and optimized sleep behavior paradigm. Specifically, the researchers have 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 researchers have presented these findings in the Cold Spring Harbor Drosophila Neurobiology meeting (Oct 3-7, 2023) and presentation was well received. The results from this progress have been summarized in a manuscript under preparation. This work has contributed to a publication in eLIFE where the researchers characterized the structural basis of Tau aggregation. The research staff have successfully carried out the project on schedule and 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: Zhang S, Zhu Y, Lu J, et al. Specific binding of Hsp27 and phosphorylated Tau mitigates abnormal Tau aggregation-induced pathology. *Elife*. 2022;11:e79898. Published 2022 Sep 1. doi:10.7554/eLife.79898.

Patents: None at the time of reporting.

6. **Grant #:** 21A24

Principal Investigator: Laura Blair, PhD

Organization: University of South Florida

Summary: The main goals of this research project are to identify molecular chaperones that alter tau seeding and release, which is implicated in Alzheimer's disease (AD) pathogenesis and may identify novel therapeutic targets. A manuscript was accepted and is in press at the International Journal of Biological Macromolecules. This original research paper describes the results of a cell-based assay that was optimized in a prior funding period to identify molecular chaperone regulators of tau seeding. This is important since tau accumulation and spreading are associated with Alzheimer's disease progression. Molecular chaperones were selected as the proteins to be screened, since the molecular chaperones are enriched with members that control protein triage. This screen identified five specific molecular chaperones that reduce tau seeding and one that significantly increases tau seeding. Interestingly, these "hits" were concentrated in one molecular chaperone family, the DnaJ/Heat Shock Protein 40s (Hsp40s). Secondary and tertiary assays of tau accumulation in separate cell lines were used to confirm the results of these assays. The data supported the prioritization of two DnaJ proteins, DnaJB1 and DnaJB6b, for the role in regulating tau accumulation. After additional assays, DnaJB6b was demonstrated to have the greatest impact on tau, specifically lower levels of DnaJB6b increased tau levels and high levels of DnaJB6 reduced tau levels. The research staff demonstrated that this may be through direct interactions through regulating the degradation of tau. The research project staff are now working to build off these exciting findings to determine the impact of DnaJB6b on tau in the brain. To do this, male and female tau transgenic mice were treated with a gene therapy to overexpress DnaJB6b or a control protein in a brain region important for learning and memory. Cognitive and pathological outcomes will be assessed. This in vivo work is ongoing over the next funding period. This work will be highly informative on whether DnaJB6b may be used as a novel therapeutic target for the treatment of Alzheimer's disease.

Follow-on Funding: Grant Title:DnaJB6 as a novel regulator of tau; Federal Agency/Institute: National Institutes of Health/National Institute on Aging; Principal Investigator: Esquivel A; Grant Term: 8/14/2023 – 8/13/2026; Submisison Date: 8/5/2022; Grant Category: NIH predoctoral Fellowship; Total Funds Requested: $114,284.00; Total Funds Awarded: $114,284.00; Status: Funded.

Collaborations: None at the time of reporting.

Journals: Esquivel AR, Hill SE, Blair LJ. DnaJs are enriched in tau regulators. *Int J Biol Macromol*. 2023;253(Pt 7):127486. doi:10.1016/j.ijbiomac.2023.127486.

Patents: None at the time of reporting.

Appendix B Fiscal Year 2022-2023 Active Grant Details
Funded Fiscal Year 2019-2020

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
20A09	Florida State University	Aaron Wilber, PhD	250,000.00	3/31/2024	No	No	Yes
20A18	University of South Florida	Saeid Taheri, PhD	250,000.00	3/31/2024	No	No	No

1. **Grant #:** 20A09

Principal Investigator: Aaron Wilber, PhD

Organization: Florida State University

Summary: 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 a new store across town), are major symptoms. Rodent models of AD also exhibit impaired navigation. For this proposal, the research team developed a spatial navigation task for mice that mimics the impairments observed in humans (getting lost in new surroundings). Scientific evidence suggests abnormal communication between two parts of the brain: the parietal cortex and hippocampus, in humans with AD. The team previously published a paper that achieved part of this proposal by showing that interactions between the parietal cortex and hippocampus during sleep are critical to forming new memories in a triple transgenic mouse model of AD, presenting with Tau and amyloid beta (Aβ) pathology. Changes in these brain interactions during sleep could cause impaired learning in AD, especially in the early stages of the disease, which the research team is assessing here. Because activity within the parietal cortex remained intact, the paper also suggests that the mechanism of impaired memory in AD is a failure to bind the components of a memory, while the individual parts of a memory may remain intact (e.g., remembering the taste of breakfast food but not where it was eaten). The research team is also using a novel approach to understand the contributions of Tau and Aβ in the hippocampus-parietal network to impaired parietal-hippocampal interactions during sleep by reversing the pathology in these brain regions. This approach uses a non-invasive treatment that has undergone human clinical trials, supported by several papers and conference reports demonstrating its effectiveness. This work is furthering understanding of the fundamental mechanisms of this new treatment approach and is critical for further improving its effectiveness in humans. In parallel, the team is confirming these findings in a second mouse model, in which the Aβ sequence is replaced with a non-mutated human Aβ sequence, to more closely mimic sporadic AD. These data suggest that getting lost in new surroundings emerges much later in these mice than in the triple transgenic mice (14 versus six months), and that impairments are observed only in female mice, not males. The team's research is relevant to public health because it enhances knowledge about the role of changes in cortical-hippocampal functional interactions and utilizes current technologies to reverse impaired learning. The proposal will expand the knowledge base and establish a new research platform for understanding impaired memory in AD.

Follow-on Funding: Federal Agency/Institute: National Institutes of Health/National Institute on Aging; Principal Investigator: Gordon; Grant Term: 3/2023 – 2/2025; Submisison Date: 7/2022; Grant Category: R03; Total Funds Requested: $100,000.00; Total Funds Awarded: $100,000.00; Status: Funded.

Collaborations: None at the time of reporting.

Journals: Simmons CM, Moseley SC, Ogg JD, et al. A thalamo-parietal cortex circuit is critical for place-action coordination. *Hippocampus*. 2023;33(12):1252-1266. doi:10.1002/hipo.23578.

Patents: None at the time of reporting.

2. **Grant #:** 20A18

Principal Investigator: Saeid Taheri, PhD

Organization: University of South Florida

Summary: 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. Researchers 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 researchers 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 researchers to tailor treatments. The research team continues advertising for patient recruitment with posting the study flyer in Tampa General Hospital (TGH) and University of South Florida (USF) Morsani College of Medicine. Phone interviews continue with more volunteers for recruiting into the study. The research team continues to recruit more patients into the study by taking informed consents. The research staff submitted a journal paper to journal of Cerebral Blood Flow and Metabolism titled, "Longitudinal BBB transfer rate dynamics in patients with vascular cognitive impairment and dementia," and are working on the next paper on "cerebral blood flow in VCID patients".The letter of intent for Bright focus grant was not accepted. The R21 application was not funded but the researchers are working on collecting more data and submitting the application as an RO1. The researchers are in touch with vascualr cognitive impairment (VCI) research centers around the nation and hope to establish a productive collaboration as some centers show interest in this research.

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

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

Appendix C: Fiscal Year 2022-2023 Completed Grant Details

Funded Fiscal Year 2021-2022

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
22A02	Florida Atlantic University	Lisa Wiese, PhD, MSN, RN, GERO-BC, PHNA-BC, CNE	250,000.00	9/30/2023	No	Yes	Yes
22A05	Mayo Clinic Jacksonville	Shunsuke Koga, MD, PhD	100,000.00	6/30/2023	No	No	Yes
22A06	Mayo Clinic Jacksonville	Mariet Allen, PhD	$100,000.00	3/31/2023	No	No	No
22A16	University of Miami	Philip Harvey, PhD	$99,887.00	9/30/2023	No	No	Yes

3. **Grant #:** 22A02

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

Organization: Florida Atlantic University

Summary: All of the study aims were met through the course of the grant. The research team was able to identify community-specific provider and system-related barriers to clinical Alzheimer's disease and related dementias (ADRD) detection and care, using open-ended qualitative interviews. The primary barrier reported by the majority of providers was the lack of time to manage persons with cognitive decline. What mattered most to them was the lack of a locally-based neurologist to whom to refer patients for managing dementia. However, four primary care providers in the intervention group were new to practice, and did not have a large patient base established. The newer providers attended the hybrid training series offered via teleconferencing weekly for six weeks. The research team were also able to test the feasibility and effectiveness of pairing local nursing students with established community health workers to increase community awareness of brain health-promoting behaviors that can decrease dementia risk. The research team found that both community residents' and health workers' knowledge of Alzheimer's disease and dementia literacy levels increased significantly in both the control and intervention groups, based on the study measures. This suggests that simply bringing updated dementia information through outreaches in rural areas does have some positive impact. Furthermore, the confidence level of providers as measured by a validated scale was low prior to the intervention, but confidence increased significantly following the training in the intervention group. One challenge was that the local state college faculty and students were not available every semester of the study, due to unexpected faculty shortages and course schedules. Researchers then compared the approach of educating providers and their office staff in partnership with area dementia clinical experts between the following two groups. Intervention Group, Arm A is composed of providers receiving education/support from neurology teams, adult gerontological nurse practitioners' assessments/recommendations, and training of office staff regarding ADRD and community resources support for patients/caregivers. Control Group, Arm B which is composed of providers receiving adult-gerontology nurse practitioner (AGNP) assessments/recommendations only, and usual practices for memory screening and referral. All providers stated the usefulness of receiving written in-depth cognitive assessments by the AGNP. Results were mixed regarding if providers would refer directly to AGNPs for patient management of ADRD. None of the 14 providers participating in the study chose in-person training or consultation. The intervention group

participated in virtual training focused on cognitive assessment and management in primary care. Both the control and provider groups increased rates of dementia diagnosis and treatment. However, the intervention group realized a statistically significant increase of 36% in rates of patients diagnosed and being treated for ADRD, compared to only 19% in the control group. In summary, partnering local nursing students with community residents, who served as research assistants, increased dementia awareness in a rural setting. Patient loads, support by AGNPs who are trained in dementia management, and participation in virtual training are key factors to consider when designing interventions to increase rates of dementia diagnosis and treatment in underserved settings.

Follow-on Funding: Federal Agency/Institute: National Institute on Aging, National Institutes of Health; Principal Investigator: Wiese L; Grant Term: 9/1/2023 – 8/31/2028; Submisison Date: 8/23/2022; Grant Category: R01/External, New Investigator; Total Funds Requested: $4,300,000.00; Total Funds Awarded: $4,200,000.00; Status: Funded.

Collaborations: In addition to Palm Beach State College students and faculty, and Florida Atlantic University undergraduate, graduate, and nurse practitioner students (as described in the previous legislative report), the researchers enhanced or added to a substantial network of collaborators as a result of this Optimizing Rural Community Health Through Interdisciplinary Dementia (ORCHID) grant, all of which included students (volunteers, interns, practicum) from various disciplines and institutions: Diabetes Coalition of Palm Beach and Martin County, Delta Sigma Theta (African American sorority), AmeriHealth Caritas Florida, Lake Okeechobee Rural Health Network, Health Care District, Palm Beach County, American Heart Association, Glades Initiative, Brother Church Radio, Legal Aid Society, Glades Area Ministerial Association, and Lakes Medical Center.

Journals: Daniel EV, Wiese LAK, Holt JK. Assessing Alzheimer's Disease Knowledge and Cognitive Risk Among a Rural Older Afro-Caribbean Cohort. *J Community Health Nurs*. Published online September 13, 2023. doi:10.1080/07370016.2023.2257199.

Rahemi Z, Malatyali A, Wiese LAK, Dye CJ. End-of-Life Care Planning in Diverse Individuals Across Age Groups: A Proposed Conceptual Model of Nursing. *J Nurs Care Qual*. 2023;38(4):319-326. doi:10.1097/NCQ.0000000000000705.

Patents: None at the time of reporting.

4. **Grant #:** 22A05

Principal Investigator: Shunsuke Koga, MD, PhD

Organization: Mayo Clinic Jacksonville

Summary: During the specified period, the research project made significant strides in the field of Alzheimer's disease (AD) and tauopathies diagnosis using digital histopathology images. The primary objective was to harness the power of machine learning to develop reliable diagnostic tools for these neurodegenerative disorders. Neurodegenerative disorders, particularly Alzheimer's disease and tauopathies, present a significant challenge in accurate diagnosis due to overlapping clinical presentations. Traditional neuropathologic examination, while considered

the gold standard, is time-consuming, expensive, and subject to variability. This research project aimed to address these challenges by developing machine learning algorithms that can analyze digital histopathology images to provide accurate diagnoses. The research project staff focused on two innovative algorithms: self-supervised learning (SSL) and weakly-supervised learning. Both techniques were chosen for the potential to deliver accurate results even when labeled data are limited. The project successfully trained the weakly-supervised learning algorithm, known as clustering-constrained-attention multiple-instance learning (CLAM), on whole-slide images of brain sections processed with tau immunohistochemistry. This approach demonstrated the feasibility of using CLAM for high-throughput analysis and diagnosis of tauopathies. Alzheimer's disease affects a significant portion of Florida's elderly population, leading to emotional, physical, and financial burdens on families and the healthcare system. By developing a reliable and efficient diagnostic tool, the research project offers the potential for earlier and more accurate diagnosis. Early detection can lead to timely interventions, better management, and improved quality of life for affected individuals and families. Furthermore, the economic implications of an efficient diagnostic tool are substantial. By reducing the time and resources spent on traditional diagnostic methods, there's potential for significant cost savings in the healthcare sector. This represents a notable return on investment for the state's funding in this research. In conclusion, the research project has made significant advancements in the field of neurodegenerative disorder diagnosis. By leveraging machine learning algorithms, the project offers a promising solution to the challenges faced in diagnosing Alzheimer's disease and tauopathies. The potential benefits to the health outcomes of Floridians and the economic implications underscore the value and importance of this research.

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

Collaborations: None at the time of reporting.

Journals: Kim M, Sekiya H, Yao G, et al. Diagnosis of Alzheimer Disease and Tauopathies on Whole-Slide Histopathology Images Using a Weakly Supervised Deep Learning Algorithm. *Lab Invest*. 2023;103(6):100127. doi:10.1016/j.labinv.2023.100127.

Koga S, Metrick MA 2nd, Golbe LI, et al. Case report of a patient with unclassified tauopathy with molecular and neuropathological features of both progressive supranuclear palsy and corticobasal degeneration. *Acta Neuropathol Commun.* 2023;11(1):88. Published 2023 Jun 1. doi:10.1186/s40478-023-01584-z

Patents: None at the time of reporting.

5. **Grant #:** 22A06

Principal Investigator: Mariet Allen, PhD

Organization: Mayo Clinic Jacksonville

Summary: Alzheimer's Disease (AD) is the most common form of dementia, accounting for around 70% of total dementia diagnoses. AD affects much more than the patients themselves; this degenerative disease requires patients are constantly cared for, affecting families and healthcare systems. AD can only be definitively diagnoses at autopsy by the presence of

accumulated amyloid-beta (Aβ) and tau proteins in the brain, the pathological hallmarks of AD. The brain is a highly complex organ comprised of numerous cell types working in concert to maintain normal neural function (homeostasis) and research has shown that the cells responsible for maintaining brain homeostasis are frequently perturbed in AD. The resident immune cells of the brain, microglia, are notorious for their dysfunction in AD. A notion that is reinforced as more research studies decipher the differences and effects of AD on brain homeostasis and specific brain cell types. Microglia have also been genetically tied to AD; large scale genetic studies have identified genetic variants in microglial-specific/enriched genes with varying impacts on AD risk. Notably, specific variants in the Aβ (rs616338-T) and PLCG2 (rs72824905-G) genes have been shown to increase the risk for, and protection against developing AD, respectively. In this project, the roles of phospholipase C-gamma-2 (PLCG2) and Aβ genetic variants were dissected in microglia cells by leveraging deeply phenotyped brain samples and single nuclei approaches. The research team generated single nucleus transcriptome data using a novel microglia enrichment protocol from frozen human brain of PLCG2 and Aβ variant carriers. After data quality control, transcriptomic profiles from nearly fifty-five thousand brain cells were retained across the 28 participants and microglia comprise 58% of the total nuclei. As microglia comprise less than 7% of all cells in recent single nucleus studies, this methodology proves effective for increasing microglia proportion. The research staff is currently conducting differential gene expression analysis. Completion of the current analyses will provide insights into molecular changes that occur in the presence of PLCG2 and Aβ variants in microglia. The team expects to identify specific pathways and mechanisms regulated by these variants. Differentially expressed genes will be explored further using additional experimental techniques in the coming months. The study of AD risk and the protection conferred by genetic variants is fundamental for identifying novel therapeutic targets. The AD research community frequently focuses on the underlying pathological mechanisms of AD, which has been effective in targeting the progression of AD pathology. However, it is important to conduct studies that aim to understand the resilience mechanisms that provide natural protection. The harmonization of results from resilience studies with those exploring pathological mechanisms allows for the identification of novel therapeutic avenues and targets, while improving the prioritization of known targets. Any therapeutics coming from this combinatorial approach to studying AD would greatly benefit the state of Florida as novel therapies for AD can improve the health of the diseased and their families. The increased health of Floridians reduces the financial burden placed on the state and healthcare 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.

6. **Grant #:** 22A16

Principal Investigator: Philip Harvey, PhD

Organization: University of Miami

Summary: Dr. Diana Hincapie served as the postdoctoral research fellow and neuropsychology trainee during the reporting period from 7/1/22 through 6/30/2023 before graduating in July 2023. Dr. Hincapie gained advanced specialty training in Alzheimer's disease (AD) and AD related disorders clinical research and grew to be a valued and integrated member of the Center for Cognitive Neuroscience and Aging (CNSA) at the University of Miami (UM). The postdoctoral fellow worked alongside a multidisciplinary team of neurologists, geriatric psychiatrists, neuropsychologist, and other specialties. Dr. Hincapie worked well with mentors, other trainees and staff. Each mentor has offered a unique and complementary opportunities. The University of Miami Brain Health Pavilion and the large National Instittues of Health (NIH)-funded clinical research program at the CNSA served as the ongoing training environment for Dr. Hincapie, as planned. This fellowship training year was focused on the development of advanced skills in clinical, cognitive, and functional assessment, research methodology, grant writing, obtaining Institutional Review Board (IRB) approval, 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 for Dr. Hincapie included the delivery of empirically supported cognitive interventions with the aim of improving brain health. Dr. Hincapie learned about various intervention strategies and became well trained in selecting interventions that personalized to the older adult, depending on their level of impairment and/or risk. Dr. Hincapie also received extensive training related to the administration, scoring, and interpretation of traditional neuropsychological assessments methods used for the detection and diagnosis of ADRD and participated in the preparation of multiple scientific conference Summarys and publications in peer-reviewed journals. Dr. Hincapie also spearheaded an independent project that was piloted in the Center related to novel plasma biomarkers and relationship to cognitive performance, particularly among Black/African American and Hispanic/Latino older adults. Dr. Hincapie assisted with overseeing operations to launch recently funded NIH and Florida Department of Health (FLDOH) research projects along with Co-Mentors, Drs Harvey, Curiel, and Loewenstein. This includes obtaining IRB approval and completing IRB modifications, preparing for the implementation of study protocols, and executing study procedures. One major contribution during the reporting period, is that Dr. Hincapie was able to direct a team to develop comprehensive coding protocols and systemically digitize crucial portions of the study. This achievement speaks to Dr. Hincapie's development as a clinical researcher and represents a growth in skillset as it relates to methodology and operational management of multi-faceted ADRD clinical research. There is an urgent need to adequately train the next generation of clinician-scientists that will contribute greatly to the health of older adult Floridians and their families. Specialists in the field of AD need to develop advanced clinical research skills to expand upon ongoing efforts aimed at the development of accessible diagnostic methods that could potentially detect AD before irreversible brain degeneration occurs. The current training opportunity is of particularly high impact, in that the field of neuropsychology plays a critical role in the diagnosis and management of ADRD.

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

Collaborations: During the reporting period, Dr. Hincapie was involved in the supervision of predoctoral practicum students from the University of Miami, Nova Southeastern University, and Albizu University using a developmental model of supervision. In this capacity, the fellow participated in the training of six graduate students in the science and practice of neuropsychology. The fellow worked with Mentors to design and implement a didactic series aligned with the Houston Conference Guidelines and provided supervision and support, as well as lectures and interactive case conferences.

Journals: Otto MW, Smits JA, Reese HE. Cognitive-behavioral therapy for the treatment of anxiety disorders. *J Clin Psychiatry*. 2004;65 Suppl 5:34-41.

Curiel Cid RE, Crocco EA, Kitaigorodsky M, et al. A Novel Computerized Cognitive Stress Test to Detect Mild Cognitive Impairment. *J Prev Alzheimers Dis*. 2021;8(2):135-141. doi:10.14283/jpad.2021.1.

Curiel Cid RE, Crocco EA, Kitaigorodsky M, et al. A Novel Computerized Cognitive Stress Test to Detect Mild Cognitive Impairment. *J Prev Alzheimers Dis*. 2021;8(2):135-141. doi:10.14283/jpad.2021.1.

Curiel Cid RE, Ortega A, Crocco EA, et al. Semantic intrusion errors are associated with plasma Ptau-181 among persons with amnestic mild cognitive impairment who are amyloid positive. *Front Neurol*. 2023;14:1179205. Published 2023 Aug 4. doi:10.3389/fneur.2023.1179205.

Curiel Cid RE, Crocco EA, Kitaigorodsky M, et al. A Novel Computerized Cognitive Stress Test to Detect Mild Cognitive Impairment. *J Prev Alzheimers Dis*. 2021;8(2):135-141. doi:10.14283/jpad.2021.1.

Hincapie D, Gilmore M, Lenox M, Stripling A. Assessment and treatment of elder abuse in Spanish speaking Americans: A scoping review. *Aggression and Violent Behavior*. 2020;57: 101480. doi: 10.1016/j.avb.2020.101480.

Patents: None at the time of reporting.

Appendix C: Fiscal Year 2022-2023 Completed Grant Details

Funded Fiscal Year 2020-2021

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
21A01	Florida Atlantic University	Monica Rosselli, PhD	$99,051.00	2/28/2023	No	No	Yes
21A03	Florida Atlantic University	Howard Prentice, PhD	$99,050.00	11/30/2022	No	No	No
21A05	Florida State University	David Meckes, Jr., PhD	$99,051.00	2/28/2023	No	No	Yes
21A07	RELINQUISHED						
21A08	University of Florida	Karen McFarland, MD, PhD	$99,051.00	2/28/2023	No	No	No
21A11	University of Florida	Barry Setlow, PhD	$247,620.00	2/28/2023	No	Yes	Yes
21A12	University of Florida	Karina Alvina, PhD	$99,051.00	2/28/2023	No	Yes	Yes
21A13	University of Miami	William (Dalton) Dietrich, PhD	$247,620.00	8/31/2023	Yes	Yes	Yes
21A14	University of Miami	Coleen Atkins, PhD	$247,620.00	4/30/2023	No	Yes	No
21A15	University of Miami	Claes Wahlestedt, MD, PhD	$247,542.00	2/28/2023	No	No	No
21A16	University of Miami	Bonnie Levin, PhD	$99,051.00	8/31/2023	No	Yes	No
21A17	University of Miami	Holly Cukier, PhD	$247,620.00	8/31/2023	No	No	No
21A18	University of Miami	Katrina Celis, MD	$99,051.00	8/31/2023	No	No	No
21A20	University of Miami	Tatjana Rundek, MD, PhD	$247,620.00	8/31/2023	Np	Yes	No
21A23	University of South Florida	Mark Kindy, PhD, FAHA	$247,620.00	8/31/2023	No	No	No
21A25	University of South Florida	Nan Sook Park, PhD, MSW	$80,000.00	8/31/2023	No	No	Yes

1. **Grant #:** 21A01

Principal Investigator: Monica Rosselli, PhD

Organization: Florida Atlantic University

Summary: During the postdoctoral training, the research fellow prepared papers for publication, including analyzing data. The fellow collaborated on writing, editing, and preparing coauthored manuscripts for submission. Additionally, the fellow was trained on theoretical issues and analysis of brain biomarkers' data obtained from volumetric brain measures, amyloid-beta depositions in the brain as reflected in polyehtylene terephthalate (PET) Scans, levels of neurofilament light (NfL), Phospho-Tau (PTAU181), Amyloid Beta (Aβ) 40 and 42 and 42/40 ratio, and glial fibrillary acidic protein (GFAP) in the blood, and reviewing relevant literature. The fellow was also trained on: dichotomous visual ratings of amyloid positivity/negativity observed on PET scans; the visual rating system for rating brain atrophy observed in structural magnetic resonance imaging (MRIs); detecting other abnormalities such as ventricular enlargement, white matter hyperintensities, infarcts, and hemorrhages and determining the appropriate MRI sequences needed in each case (i.e., magnetization-prepared rapid acquistion gradient echo (MPRAGE), fluid-attenuated inversion recovery (Flair) and susceptibility weighted imaging (SWI)). The fellow worked with the 1Florida Alzheimer's Disease Reseach Center (1FL DRC) data core on ensuring data reliability and Intersite diagnosis reliability processes, directly with the data core leader, Michael Marsiske (University of Florida (UF)). The fellow prepared case reports for biweekly clinical consensus conferences, which focus on diagnosis on a case-by-

case basis, incorporating clinical, neuroimaging, neuropsychological, and biomarkers data. The fellow attended regular meetings and collaborated in grant writing and submission.

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

Collaborations: None at the time of reporting.

Journals: Arruda F, Rosselli M, Mejia Kurasz A, et al. Stability in cognitive classification as a function of severity of impairment and ethnicity: A longitudinal analysis. *Appl Neuropsychol Adult*. Published online July 3, 2023. doi:10.1080/23279095.2023.2222861.

Patents: None at the time of reporting.

2. **Grant #:** 21A03

Principal Investigator: Howard Prentice, PhD

Organization: Florida Atlantic University

Summary: Oxidative damage and mitochondrial dysfunction are accepted as major factors responsible for hypoxic injury and Alzheimer's disease (AD) pathogenesis but there are no effective therapeutic strategies to utilize these mechanisms for the development of new drugs. Hypoxia was previously shown to elicit increased production of beta amyloid (Aβ) and dysfunction in tau proteins which also leads to neuronal death by increasing free radical formation and oxidation responses. Recent studies have demonstrated that sulindac protects against hypoxic/ischemic damage through eliciting anti-oxidant and pro-survival processes. This research enabled evaluation of sulindac in its suitability for reversing the pathophysiological characteristics of AD and hence will have a direct impact on clinically related decisions regarding the potential use of sulindac in the treatment of Alzheimer's disease. The current study investigated whether sulindac would protect against Aβ aggregation and dysfunctional tau phosphorylation using an in vitro cell culture and an in vivo transgenic mouse model of AD. The researchers aimed to characterize and measure the effect of sulindac on Aβ aggregation and tau hyperphosphorylation in SH-SY5Y amyloid precursor protein's (APP) overexpressing neuronal cells under hypoxic conditions. Their research in this regard resulted in establishing an in-vitro model in SH-SY5Y cells with overexpression of mutant APP (Swedish mutation) and validating the mutant APP expression using western blots. By assessing cell proliferation at different time points six, 12 and 24 hours of hypoxia, it was possible to optimize the incubation - time under normoxia and hypoxia for both transfected and un-transfected SH-SY5Y cells. It was demonstrated that treatment with sulindac protected against cell death in hypoxia in transfected SH-SY5Y cells. The researchers then tested the effect of chronic treatment with sulindac in Aβ aggregation in an AD mouse model when subjected to hypoxia. In addition, an important collaboration was set up with Dr. Hung Wen (Kevin) Lin, Louisiana State University, Shreveport, Louisiana. Dr. Lin had financial support from grants to carry out key experiments on an Alzheimer's mouse line (3xTg-AD; Jackson Labs) as well as exposure of mice to hypoxic conditions. 3xTg Alzheimer's mice were subjected to hypoxia with and without administration of sulindac. Cerebral blood flow was assessed using laser speckle contrast imaging and behavioral measurements included assays of working /short term memory as well as

reference/long term memory. Reduced cerebral blood flow was shown by laser speckle contrast imaging to decrease in aged female 3xTg-AD mice. Furthermore, neurogenic locus notch homolog protein 1 (NOTCH1) protein expression was decreased in the brain of aged 3 x Tg-AD female mice. Impaired functional learning/ memory was also analyzed using T-maze and novel object recognition test respectively. A decrease was found in spontaneous alternation ratio as well as number of entries in the novel zone in aged 3xTg-AD female mice relative to controls. Aged female 3xTg-AD mice showed higher presenilin protein expression than aged control mice. Following sulindac administration to young 3xTg-AD mice it was shown that sulindac increased expression in the cortex of alpha and beta-secretase but reduced expression of gamma-secretase.

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

Collaborations: A collaboration is ongoing on Alzheimer's disease mice with Louisiana State University, Shreveport, Louisiana. The experiments involve testing of 3xTg Alzheimer's mice (Jackson Labs.) subjected to hypoxia with and without administration of sulindac. Cerebral blood flow was assessed using laser speckle contrast imaging and blood brain permeability changes were determined by measurement of Evan's blue penetration into the brain. Behavioral measurements were carried out for assessment of working /short term memory as well as novel object recognition for reference and long term memory.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

3. **Grant #:** 21A05

Principal Investigator: David Meckes, Jr., PhD

Organization: Florida State University

Summary: Recent publications suggest that small ribonucleic acid (RNA) and other molecules can be introduced into Extracellular Vesicles (EVs) by sonication, electroporation, polyethelene glycol (PEG) induced liposome fusion and other methods. The hypothesis is that the therapeutic function of human marrow stem cell (hMSC) three dimensional (3D) EV will be enhanced by loading specific small RNAs or compounds. Research project staff will attempt to improve the therapeutic properties of hMSC EVs by loading them with anti-inflammatory and neuroprotective compounds (curcumin and cannabidiol (CBD)) and micro (mi)RNAs. This will be accomplished by engineering hMSCs to overexpress neuroprotective or anti-inflammatory miRNAs (miRNA1-32, miRNA-21, miRNA- 29-ab and proteins (IL-10 and IL4); and packing EVs with neuroprotective compounds. The engineered EVs will be tested using in vitro immunological and neurotoxicity assays. To comparing loading efficiency with electroporation, same amount of EV incubated with CBD without electroporation was used as control. Based on the results of Nano particle tracking assay (NTA), protein and CBD quantification results, there is no significate difference between the control group and electroporation group. These results show that electroporation may not be necessary for CBD loading, small molecules will bind or insert into EVs under incubation at room temperature. In another study, hsa-miR-21 was used

because it is highly expressed and upregulated in 3D hMSC EVs in previous results. And also, it is the most investigated microRNAs which plays a crucial role in diseases including development, cancer and inflammation. After electroporation, hsa-miR-21 level has about 28000-fold increase comparing with the unloading control. Moreover, RNase treatment could prove successfully loading into hMSC EVs, which is important for stability and delivery efficiency in the in vivo environment. NTA and protein quantification results show about 60% recovery with EV marker protein maintained after electroporation. To test the function of these miR-21 loaded EVs, microglia cells had been used. hMSC EV inhibition on microglia can be recovered by miR-21 loading. After two-days treatment of hsa-miR-21 loaded or control hMSC EVs, significant inhibition on cell growth was observed and miR-21 had reversed this effect. hMSC EVs have been found to exhibit anti-inflammatory, anti-apoptotic, and neuroprotective properties. It is thought that EV-based therapies could directly lead to new classes of drugs and clinical trials are currently underway for diverse diseases. As effective treatments for AD are lacking, new options would greatly improve the quality of care and reduce AD morbidity and mortality in Florida. This project aims' seek to test the potential utility of MSC-EVs in AD treatment and further enhance the neuroprotective properties of MSC-EVs. These advances have great potential to result in new therapeutic avenues to treat AD and other neuroinflammatory-based disease. As Alzheimer's disease prevalence is increasing in Florida, there is a great need for new treatments.

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

Collaborations: The collaborators on this project at Florida State University (FSU) and at Florida A&M University (FAMU) have continued to characterize, optimize and validate data on the loading of extracellular vesicles from hMSC-derived EVs. One of the project collaborators (Dr Yan Li) has continued to make substantial progress on the EV technology and associated assays (see the new published manuscript below). This research group is continuing to optimize efficient loading protocols, to enhance miR qPCR assays, to refine tests for the effects of EVs on leukocyte biology, and to validate neurotoxicity assays as proposed in this project. Project collaborators include: FAMU, College of Pharmacy & Pharmaceutical Sciences (Dr. M. Sachdeva) and a grad student, FSU, Dept of Chemical & Biomedical Engineering (Dr. Yan Li) and grad student, and the FSU, College of Medicine (Dr J. Olcese, Dr. Yi Ren, Dr. Li Sun, and a grad student.

Journals: Muok L, Liu C, Chen X, et al. Inflammatory Response and Exosome Biogenesis of Choroid Plexus Organoids Derived from Human Pluripotent Stem Cells. *Int J Mol Sci*. 2023;24(8):7660. Published 2023 Apr 21. doi:10.3390/ijms24087660.

Patents: None at the time of reporting.

4. **Grant #:** 21A08

Principal Investigator: Karen McFarland, MD, PhD

Organization: University of Florida

Summary: More than six million people are living with Alzheimer's disease (AD) in the United States and that number is projected to more than double by 2060 causing an immense societal and economic burden. Understanding how the accumulation of amyloid beta (Aβ) protein into amyloid plaques and Tau protein into neurofibrillary tangles, pathological hallmarks of AD, lead to neurotoxic effects are critical to the development of effective treatments.This grant focused on how the abnormal accumulation of Aβ affects the epitransriptome. The epitranscriptome describes the dynamic modification of methyl groups to nucleosides of ribonucleaic acid (RNA) transcripts which are the precursors for protein production. These modifications are reversible and are thought to allow for rapid changes in protein levels. This mechanism would then allow a cell to rapidly respond to environmental cues. N6-methylation at adenosine residues (m6A) are present in the mammalian brain and levels of enzymes that are responsible for the addition and removal of are altered in the brains of amyloid mouse models. The epitranscriptome was examined in two datasets obtained from the RNA extracted from amyloid models. In the first, microglia, a specialized neuroglia cells in the brain that acts as the brain's immune system, were cultured from mouse brains and the treated with monomeric, oligomeric or fibrillar forms of Aβ protein alongside untreated controls. RNA extracted from the brains of an amyloid mouse model at an advanced stage of disease was used. Because of the low yields of RNA in the first experiments, the alternative technology of MinION flowcells from Oxford Nanopore Technology was used to sequence the RNA to detect the m6A residues. The MinION flowcells utilizes nanopores embedded in a membrane to sequence RNA. As the RNA passes through the nanopore, the base composition of the RNA sequences of the RNA changes the electrical current as it passes through. Furthermore, RNA can be place directly on nanopore flowcells and amplification in signal is not necessary; therefore, the RNA-and any modified bases-can be natively identified by the altered electrical current. The resulting long-read sequence data from both experiments was compared to pre-existing short-read datasets from similar experiments to assess the quality of the new data. Differentially expressed genes identified between experimental and control groups were fit to a linear model which demonstrated a moderate correlation between the two datasets. This indicates the data is of sufficient quality. However, the challenge then remains in identifying the modified base embedded within the electrical signal. Attempts at using published, existing algorithms, such as Epinano, did not produce good results. Institutional computing help at the University of Florida (UF) HiPerGator indicated that the support from the original publisher for this software was lackluster. In the end, the detection of modified RNA bases in these AD model systems failed for this reason. While this is disappointing, newer software packages to detect modified RNA bases are being published and released. Despite this, these datasets have great potential and are a valuable tool for using on newer software analysis packages.

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 #:** 21A11

Principal Investigator: Barry Setlow, PhD

Organization: University of Florida

Summary: The overall goal of this project was to use rodent models to determine how cannabis (marijuana) affects Alzheimer's disease (AD) pathology and cognitive function in aging. Experiments under Aim 1 were designed to determine how chronic exposure to cannabis smoke affects the progression of one form of AD pathology (tau expression) and inflammatory markers in a mouse model. Results under this Aim to date show that the smoke exposure model produces levels of tetrahydrocannabinol (THC) comparable to those achieved in human cannabis users (published in Gazarov et al. 2023, Frontiers in Pharmacology) and that chronic exposure to cannabis smoke causes an increase in circulating levels of the inflammatory protein chemokine (C-C motif) ligand 5 (CCL5) in aged but not young adult mice. As increased levels of CCL5 are associated with both aging and AD, these data could suggest that cannabis has detrimental effects on the inflammatory environment in older adults, although additional work is needed to follow up on this finding. Further experiments assessing the effects of chronic exposure to cannabis smoke on brain inflammation and tau pathology have been conducted, and analyses of data from these experiments are still ongoing. Experiments under Aim 2 were designed to determine how chronic exposure to cannabinoids affects cognitive function in an aged rat model. Results under this Aim show that chronic oral consumption of a low dose of delta-9-THC, (the primary psychoactive component of cannabis) enhances working memory in aged rats but has no effects on working memory in young rats (i.e., it reverses age-related working memory deficits). In contrast, the same oral THC consumption regimen fails to influence spatial learning and memory in either young adult or aged rats, despite the presence of deficits on this form of cognition in aged compared to young adult rats. Considered together, the results of Aim 2 suggest that chronic exposure to a low dose of THC has the potential to reverse some forms of age-related cognitive impairment. In combination with the forthcoming data from Aim 1, these data will provide a comprehensive overview of potential risks and benefits associated with cannabis use in older adults.

Follow-on Funding: Grant Title: A translational animal model to study neurobehavioral consequences of THC and oxycodone polysubstance use; Federal Agency/Institute: Florida Consortium for Medical Marijuana Clinical Outcomes Research; Principal Investigator: Knackstedt L; Grant Term: 7/1/22-6/30/23; Grant Category: Regular Grant; Total Funds Requested: $74,998.00; Total Funds Awarded: $74,998.00; Status: Funded.

Collaborations: College of Medicine, Department of Psychiatry (Dr. Barry Setlow, Emely Gazarov). College of Medicine, Department of Neuroscience (Dr. Jennifer Bizon, Dr. Jada Lewis, Sabrina Zequeira) College of Pharmacy, Department of Medicinal Chemistry (Dr. Chris McCurdy). College of Pharmacy, Department of Pharmaceutics (Dr. Abhisheak Sharma, Erin Berthold, Alexandria Senetra).

Journals: Gazarov EA, Zequeira S, Senetra AS, et al. Pharmacokinetics of delta-9-tetrahydrocannabinol following acute cannabis smoke exposure in mice; effects of sex, age, and strain. *Front Pharmacol*. 2023;14:1227220. Published 2023 Aug 28. doi:10.3389/fphar.2023.1227220.

Patents: None at the time of reporting.

6. **Grant #:** 21A12

Principal Investigator: Karina Alvina, PhD

Organization: University of Florida

Summary: The researchers used a mouse model of Alzheimer's disease (AD) (mouse strain called CRND8) and successfully conducted an exercise protocol (daily swimming for three weeks) and performed several behavioral tasks to probe memory function and exploratory behaviors. The research team also collected a variety of tissues to later evaluate different patterns of protein or transcriptional expression. Researchers are currently in the process of analyzing the data collected. In addition, the research team established a new collaboration with Dr Kyle Allen, Associate professor in Biomedical Engineering, from the College of Engineering at University of Florida (UF). Researchers finished the second cohort of AD mice placed in running cages for eight weeks and another group that ran for four weeks. These male mice ran on a voluntary basis using running cages designed by the Allen lab. The results showed different patterns of body weight changes in different conditions. Importantly, AD mice that exercise showed less anxiety like behaviors and changes in adrenal glands size. The researchers are currently analyzing protein expression of Irisin in circulation and in other tissues. In addition, researchers ran a third cohort with female AD transgenic mice and are in the process of analyzing data collected. Researchers have continued to evaluate different antibodies using both mouse brain and muscle tissue as controls to find the most effective one and use to stain human brain samples as proposed. The research team tried two different commercial sources for the antibody and spent significant efforts troubleshooting the methods to get the best staining results. So far, these antibodies have not produced the expected results and thus have used western blots as an alternative to measure protein expression in mouse brain tissue. The researchers have seen very interesting results comparing different brain regions and conditions (sedentary vs exercise). These results have shown that the expression of fibronectin type III domain-containing protein 5 (FNDC5) and Irisin is different when comparing different brain areas such as olfactory bulb and hippocampus in conditions of exercise or sedentary lifestyle in young adult male mice. The researchers are following up on these results and including groups of sedentary and exercised mice as well as expanding these experiments to use female mice.

Follow-on Funding: Grant Title: Dissecting the role of the "muscle-brain axis" in promoting resilience to stress and neuroprotection; Federal Agency/Institute: The Joe W. and Dorothy Dorsett Brown Foudnation; Principal Investigator: Alvina K; Grant Term: 6/1/2022 – 5/31/2023; Submisison Date: 4/15/2022; Grant Category: Neuroscience Basic Science Program; Total Funds Requested: $15,000.00; Total Funds Awarded: $15,000.00; Status: Funded.

Collaborations: The researchers are actively collaborating with members of the UF Department of Biomedical Engineering and also the Center for Translational Research in neurodegenerative disorders (CTRND).

Journals: Hamed MF, Enriquez V, Munzen ME, et al. Clinical and pathological characterization of Central Nervous System cryptococcosis in an experimental mouse model of stereotaxic intracerebral infection. *PLoS Negl Trop Dis*. 2023;17(1):e0011068. Published 2023 Jan 19. doi:10.1371/journal.pntd.0011068.

Patents: None at the time of reporting.

7. **Grant #:** 21A13

Principal Investigator: William (Dalton) Dietrich, PhD

Organization: University of Miami

Summary: 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, evidence for TBI accelerating the emergence and severity of AD-like pathologies has been proposed. The central hypothesis is that an increase in neuroinflammation in AD augments TBI-induced inflammation and contributes to memory impairments in models of AD. The first aim which has been completed during this past year investigated the temporal activation and cellular distribution of TBI-induced inflammasome activation on AD pathology. After injury in AD transgenic mice, protein analysis of cortical tissue showed significantly increased activate (cleaved) caspase-1, caspase-8, and IL-1 when compared to shams at one hour post injury and maintained at one day and at one week post injury. These findings provide evidence for brain injury resulting in increased neuroinflammatory activity which was maintained over the course of one week after injury. This increase was not seen in hippocampal tissue which is a structure involved in learning and memory. To determine whether AD predisposition impacts the neuroinflammatory response to TBI, protein analysis was performed in cortical tissue from wildtype (WT) and AD mice at one day post injury or sham surgery. The findings showed increased IL-1 after brain injury in AD mice when compared to brain injured WT mice. There were significant increases of levels of activated caspase-1, caspase-8, and IL-1 in WT and AD mice after controlled cortical impact (CCI) compared to sham controls. The drug IC100 reduces inflammasome protein expression in AD mice after TBI. To assess alterations in cognitive function after brain trauma in AD and WT mice, mice were tested in open field at three days post-surgery and novel object recognition at 14 days post-surgery. Although there was some increased anxiety behavior in the AD mice after trauma, there were no differences in cognitive function using the novel object recognition test. Overall, the findings indicate that TBI increased inflammasome activation in mice with a genetic predisposition towards AD. These findings are further evidence that a treatment targeting neuroinflammation has the potential to reduce the development of AD after TBI in the clinic.

Follow-on Funding: Grant Title: The Importance of Abnormal Inflammasome Activation as a Risk Factor between Traumatic Brain Injury and Alzheimer's Disease; Federal Agency/Institute: National Institutes of Health/National Institue of Neurological Disorders and Stroke; Principal Investigator: Dietrich D, de Rivero-Vaccari P; Grant Term: 9/20/2021 – 8/31/2026; Submisison Date: 3/4/2021; Grant Category: RF1; Total Funds Requested: $4,566,317.00; Total Funds Awarded: $4,566,317.00; Status: Funded.

Collaborations: None at the time of reporting.

Journals: Johnson NH, Hadad R, Taylor RR, et al. Inflammatory Biomarkers of Traumatic Brain Injury. *Pharmaceuticals* (Basel). 2022;15(6):660. Published 2022 May 25. doi:10.3390/ph15060660.

Johnson NH, de Rivero Vaccari JP, Bramlett HM, Keane RW, Dietrich WD. Inflammasome activation in traumatic brain injury and Alzheimer's disease. *Transl Res*. 2023;254:1-12. doi:10.1016/j.trsl.2022.08.014.

Vontell RT, de Rivero Vaccari JP, Sun X, et al. Identification of inflammasome signaling proteins in neurons and microglia in early and intermediate stages of Alzheimer's disease. *Brain Pathol*. 2023;33(4):e13142. doi:10.1111/bpa.13142.

Patents: de Rivero Vaccari JP, Keane RW, Dietrich WD, et al, inventors; Inflammatory Biomarkers of Traumatic Brain Injury. (UMIP-754 & UMIP-770). US 63/334,218 (provisional) (04/25/2022).

8. **Grant #:** 21A14

Principal Investigator: Coleen Atkins, PhD

Organization: University of Miami

Summary: Traumatic brain injury (TBI) and Alzheimer's disease (AD) are significant public health problems in Florida. In 2020, there were 21,540 hospitalizations related to TBI in Florida and there are approximately 370,000 Floridians living with long-term disabilities from TBI. It is estimated that there were 580,000 people diagnosed with AD in Florida in 2020 and this number is projected to increase 24.1% to 720,000 in 2025. TBI is a risk factor for AD, but how TBI is linked to the development of AD is unclear. Given the prevalence of AD in the aging Floridian population, understanding how a TBI that accelerates cognitive deficits related to AD is important. The goal of this research study was to determine if TBI accelerates cognitive dysfunction in mouse models of AD and develop new drug treatments to improve recovery after TBI and AD. Mice were studied that have gene mutations that result in early onset AD. These mice have mutations in amyloid precursor protein and presenilin 1 (APP/PS1), which accelerates beta-amyloid deposition mice. Another set of mice studied have mutations in amyloid precursor protein and presenilin 1 as well as tau (3xTg-AD mice). AD mice and their wild type controls received sham surgery or mild controlled cortical impact at two months of age (presymptomatic for AD) or at 12 months of age (symptomatic stage). Mice were treated with an anti-inflammatory drug, T2409, which inhibits phosphodiesterase 4B or BAY 60-7550, which inhibits phosphodiesterase 2. After treatment, mice were analyzed in learning and memory

tasks to study cognitive decline. Research staff were blinded to the animal genotype, surgery allocation and treatment during behavioral testing and analyses. Memory deficits were observed two-month-old APP/PS1 mice that had received a mild TBI. These cognitive impairments were rescued by treatment with T2409 or BAY 60-7550. These results indicate that the combination of TBI in the context of AD predisposition accelerates cognitive decline which can be mitigated by a phosphodiesterase 2 or 4B inhibitor. Phosphodiesterase 2A is the most prevalent of phosphodiesterases broadly expressed in the frontal and temporal cortex and hippocampus, forebrain brain regions susceptible to TBI and amyloid beta insults that precedes the spread of AD pathology. The phosphodiesterase 2A (PDE2A2) isoform contains a 17 amino acid sequence that localizes it to the mitochondria, where it is the primary regulator of cyclic nucleotide signaling in mitochondria. Mitochondrial dysfunction is an early and prominent feature of AD and TBI associated memory deficits. Recent studies found impaired mitochondrial nucleoid deoxyribonucleic acid (DNA) homeostasis, oxidative phosphorylation, and neurodegeneration in brains from patients with AD and mouse models of AD after TBI. These results demonstrate that inhibition of PDE2A2 with BAY 60-7550 may be a new therapeutic approach to reduce mitochondrial dysfunction and inflammation in the presymptomatic phase of AD. Findings from this study have the potential to impact the health of Floridians by improving cognitive functioning and slowing underlying AD-associated pathology after a mild TBI.

Follow-on Funding: Grant Title: Defining PDE2A directed mitochondrial dysfunction in traumatic brain injury-related Alzheimer's disease; Federal Agency/Institute: New Jersey Commission on Brain Injury Research; Principal Investigator:Xu Y, Atkins C; Grant J; Grant Term: 4/1/2023 – 3/31/2026; Submisison Date: 10/3/2022; Grant Category: Individual; Total Funds Requested: $540,000.00; Total Funds Awarded: $540,000.00; Status: Funded.

Collaborations: Dr. Ying Xu and Dr. Coleen Atkins collaborated on a grant proposal submitted to the New Jersey Commission on Brain Injury Research that was successfully funded. This collaboration and grant submission included critical, needed preliminary data obtained from this project. In prior studies, Dr. Xu established that PDE2A2 is localized to the mitochondrial matrix and levels of PDE2A2 are increased in Alzheimer disease mice. When levels of PDE2A2 are increased, mitochondrial functioning is impaired, resulting in decreased oxidative phosphorylation, adenosine triphosphate (ATP) levels, and increased inflammation and cell death. Work performed in this project contributed to the collaboration by demonstrating that traumatic brain injury in presymptomatic AD mice worsened cognitive deficits and these cognitive deficits were rescued by treatment with a PDE2A2 inhibitor. This collaboration has expanded the understanding of how TBI and AD interact to worsen brain pathology and functioning and identify a new therapeutic target, PDE2A2, to improve recovery.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

9. **Grant #:** 21A15

Principal Investigator: Claes Wahlestedt, MD, PhD

Organization: University of Miami

Summary: The mechanisms that drive the sexual dimorphism observed in Alzheimer's Disease (AD) are not well understood. This project aims to identify epigenetic mediators linking female sex and aging to AD. Based on the data collected by the research team, this study will highlight the need for 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. Context and progress to date: Women represent two-thirds of AD cases, and experience more rapid cognitive decline and worse pathology than men, for reasons that remain unknown. One hypothesis for the higher prevalence of AD in women lies in the drastic changes in sex hormones women experience as 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 research team 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 amyloig beta (Aβ) begin 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 in the brains of women, a factor that has been implicated in AD, also commences in peri-menopause. Since October 2021, the research staff has established a mouse model to facilitate the investigation of the menopause transition in the context of AD. In that model, accelerated ovarian failure is induced, which recapitulates the human condition better than the commonly used ovariectomized models. The research staff has validated the model at the follicle stages, replicating the early stages of menopause. The research team has also demonstrated that at the post-menopause stage, triple transgenic AD mice present impaired glucose tolerance when compared to age-matched controls and peri-menopause AD mice. Studying epigenetic changes that are occurring in the brain during the neuroendocrine state of peri-menopause, using this model, might be key to understanding AD onset in women. To date, no rodent studies have studied epigenetic modifications in the brain during the peri-menopausal state. Therefore, these studies propose to uncover the acetylation and gene expression changes occurring in the brain in peri- and post-menopause-like states in this mouse model, with the long-term goal of being able to develop more personalized or sex-specific treatments to AD. Studies are underway to complete the aims of the grant. 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 intervention may help delay AD symptoms, but early biomarkers are lacking. Through the work proposed here, the role of menopause-transition-mediated changes occurring in the brain could be key to understanding AD onset in women and may improve early AD detection in a sex specific manner, in Florida and beyond.

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

Collaborations: The Principal Investigators, two scientists and two graduate students all at the University of Miami Miller School of Medicine, as well as two undergraduate students from the

University of Miami Coral Gables campus have been involved with this research project for the reporting period.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

10. **Grant #:** 21A16

Principal Investigator: Bonnie Levin, PhD

Organization: University of Miami

Summary: The research team developed the methodology for the pilot study, established partnerships with Latinx community leaders, developed the educational protocol, and began to test its feasibility in the memory disorders clinic. This led to the creation of a clinical tool to assess vulnerability to deception. The scam scenarios underwent many revisions to make them relatable and easy to comprehend by those with cognitive impairment. The team developed other questionnaires: a demographic survey to assess one's perceived level of vulnerability and knowledge of scamming, and pre and post intervention questionnaires evaluating whether the proposed intervention increased awareness and understanding of scamming risk. All forms were translated from English to Spanish (and back translated). In addition, the Assessment of Situational Judgment, a measure originally developed by the research team (Getz and Levin) and then patented and normed (Getz, Levin, and Galvin). This paper was recently submitted for publication (under review). The Spanish translation is first comprehensive measure evaluating vulnerability to deception for non-English speaking residents in Florida. During Year 1 the team developed its mindfulness intervention protocol, translated it into Spanish and began administering shortened versions to patients to assess feasibility. In Year 2 and during the No Cost Extension, the training intervention was further refined and piloted for Latinx and non-Latinx mild cognitive impairment (MCI) patients/caregivers and individuals with MCI living alone in the community. The research team produced an impactful examiner guided educational module designed to encourage participant interaction, emphasizing fraud awareness and prevention. This module was examiner-guided, as it was designed to encourage participant interaction. The presentation covered types of real-life scams, red flags and warning signals and fraud resources. A novel training intervention, SCAM, offered steps following a mindfulness framework to guard oneself from becoming a victim of fraud. During screening, the researchers found patients and caregivers were unwilling to commit to multiple training sessions and the participant burden was too high. As a result, two major changes were incorporated: A newer, shorter educational and training intervention for the Zoom platform and a community presentation designed to increase scam awareness as well as increase participant research recruitment to compensate for recruitment difficulties resulting from the pandemic and drop out of key personnel linked to recruitment. During the last six months, the team recruited participants with MCI/early Alzheimer's disease (AD), compiled and cleaned data, performed basic analyses. A particularly important accomplishment is that, because of the pilot program, researchers were able to incorporate the training module to address a major objective in the recently funded, Florida Department of Health (FL DOH) Consortium grant entitled, Florida Consortium to Reduce Misinformation and Exploitation in Alzheimer's Disease, a multi-site

collaboration between the University of Central Florida, University of Florida, and University of Miami. In conclusion, despite many challenging hurdles associated with the pandemic, as well as the short time frame allotted for this pilot, the team created a successful and innovative bilingual educational module and training/ intervention program that will inform and protect the most vulnerable elderly with cognitive impairments against becoming a victim of fraud.

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 #:** 21A17

Principal Investigator: Holly Cukier, PhD

Organization: University of Miami

Summary: Alzheimer's disease (AD) is the leading cause of dementia in the elderly. In addition, AD occurs at a higher rate in diverse populations, being twice as frequent in African Americans (AA) and one and a half times as frequent in Hispanics relative to non-Hispanic white (NHW) populations. This discrepancy occurs even for individuals living within the same community. Moreover, these underserved populations with AD are often diagnosed at later stages of disease and less likely to receive treatments, perpetuating health disparities. However, the vast majority of AD research to date has focused on NHW populations, potentially reinforcing existing disparities. The research staff identified a 44 base pair frameshift deletion (p.Arg578Alafs*168) in the adenosine tryphosphate (ATP)-binding cassette, sub-family A (ABC1), member 7 (ABCA7) gene significantly associated with disease in AA (p=1.41x10-5, Cukier et al, 2016) and unique to populations with African ancestry. While ABCA 7 has been implicated in AD across populations, this gene has a higher effect in AA compared to NHW. Given the high prevalence of the deletion in AA (-10%) and the strong likelihood of disrupting protein function, deciphering its involvement in AD pathogenesis could lead to a breakthrough. For this project, researchers have successfully demonstrated that the African-specific 44 base pair deletion does generate a stable truncated protein that is localized to the cell membrane. This could have consequences for the function of how the deletion is increasing AD risk. As well as having loss of the wild type, full length protein, there may be an additional gain of fuction/dominant negative consequence from this truncated protein accumulating in the cells. For the in-house derived Induced pluripotent stem cell (iPSC) lines, there were issues with the cells being grown on mouse embroyic fibroblasts (MEFs), so researchers attempted to transition the lines to feeder free matrixes (ie: vitronectin/Matrigel). Other lines did not transition, and were reprogrammed again from peripheral blood mononuclear cells (PBMCs). One of these cell lines are being written up for a short lab resource paper in Stem Cell Research. The research staff also acquired an additional control iPSC line from the University of California, Irvine Alzheimer's Disease Resource Center (ADRC) for these experiments. While researchers attempted to generate 3D organoids with and without the ABCA7 deletion, staff attempts were unsuccessful.

The research staff established a collaboration with Zane Zeier's laboratory, who also has experience generating organoid models and are in the process of making organoids with and without the deletion. These will be morphologically evaluated and utilized for single cell ribonucleic acid (RNA) sequencing analysis. Through the experiments outlined in this proposal, the research team aims to elucidate the function of ABCA 7 and its potential role in cellular mechanisms that drive AD pathogenesis. Furthermore, by utilizing single cell expression data available from three dimensional (3D) organoids, this study could identify shared and unique pathways of disease and thereby provide a broader understanding of AD pathogenesis.

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

Collaborations: None at the time of reporting.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

12. **Grant #:** 21A18

Principal Investigator: Katrina Celis, MD

Organization: University of Miami

Summary: The goal of this grant was to understand the functional effect of the Asp238Glu alteration in the UNC13B gene in a Hispanic population with Alzheimer Disease (AD). This Asp238Glu alteration was identified as the most likely signal from a region in chromosome 9 responsible for the association found in the development of AD in a Hispanic population. In addition to the UNC13B gene, this region in chromosome 9 contains 600 other genes that could play a role in this association. The research staff used induced pluripotent stem cells (iPSCs) from AD and cognitively normal individuals (carrying and not carrying the Asp238Glu alteration) to generate forebrain neurons. These neurons were then assessed for AD phenotype using amyloid beta (Aβ) assays, genetic expression profiles using Bulk ribonucleic acid (RNA) sequencing and chromatin structures by performing in-situ Hi-C. The research staff have successfully completed all aims of the grant with interesting and promising results. This project generated nine iPSCs, nine neuronal progenitor cells (NPCs) and seven forebrain neuronal lines from seven Hispanic White and two NonHispanic White individuals. These lines were confirmed to be successfully reprogrammed and differentiated using quality control measurements including immunocytochemistry (ICC) and quantification of iPSC, NPC and neuronal markers. The research indicated that Aβ40 and Aβ42 levels are age-dependent even in cognitive normal individuals, supporting previous evidence. The team also demonstrated an increased Aβ40/Aβ42 ratio at day 75 compared to day 60 of neuronal maturation, which has been reported to drive tau pathology in neural cell models of AD. Transcriptomic profiles from Bulk RNA sequencing and chromatin structure analysis from in situ Hi-C experiments, showed that UNC13B expression was not significantly different between carriers and noncarriers of this alteration, with or without AD, which rejected the initial hypothesis. However, a decreased expression of ACO1 (Acotinase 1) gene in AD individuals was found. The ACO1 gene is involved in iron regulation inside the cell and translation suppression of APP. Interestingly,

decreased expression in ACO1 has been reported in peripheral blood mononuclear cells (PBMCs) from AD individuals. Iron homeostasis have been reported to affect many important aspects in the development of AD, including changes in metabolism, oxidative stress and hypoxia and inflammation, which makes ACO1 gene and potential gene involved in AD pathogenesis. Part of the data generated in this project was included as a reference data in a study that found a susceptible AD region in Chromosome 1 in another Hispanic population (Peruvian). In conclusion, this grant allowed us to narrow down an AD region previously reported and identified a potentially new candidate gene involved in the development of AD in a Hispanic population. The Alzheimer Association statistics revealed that the amount of AD cases in the state of Florida is projected to increase 24.1% from 2020 to 2025. The percentage of Hispanic individuals living in Florida is around 27%, a population with a high incidence of AD (13% over 65 are diagnosed with AD).

Follow-on Funding: FDOH, $99,051.00

Collaborations: None at the time of reporting

Journals: None at the time of reporting.

Patents: None at the time of reproting.

13. **Grant #:** 21A20

Principal Investigator: Tatjana Rundek, MD, PhD

Organization: University of Miami

Summary: The research team performed high-resolution carotid ultrasound imaging in 64 participants enrolled to the 1FL ADRC. The team analyzed carotid IMAGINE measures of arterial wall structure including carotid intima-media thickness (cIMT), presence of carotid plaque and characterization of carotid plaque area, the Gray Scale Median (echodensity index), geometry (common-to-internal carotid artery angle), and assessment of endothelial function (arterial stiffness, blood flow velocity-BFV). The study showed a high prevalence of atherosclerotic plaque, and overall burden of carotid disease, especially among participants from minority backgrounds and among carriers of the APOE4 allele. Research staff spent significant time analyzing MRI images for volumetric parameters of markers of cerebral small vessel disease, including white matter hyperintensity volume (WMHV), silent brain infarcts (SBI), microbleeds (CMB), and enlarged perivascular spaces (PVS), markers of neurodegeneration (cortical atrophy in AD prone regions) and amyloid load analyses. This also included completing a consensus of Fazekas rating scales (a widely used method to visually rate hyperintense white matter signal abnormalities in MRI data). Programing codes were completed and implemented pending measuring the IMAGINE markers; focus will be on relating the final reads with other phenotypes and biomarkers. Researchers correlated age-related arterial stiffness with cognitive function using a measure of arterial stiffness estimated from age and blood pressure- estimated pulse wave velocity (ePWV). A sample (mean age 68±9 years, 60% women; 67% Hispanic, 18% non-Hispanic Black, 15% non-Hispanic White participants), the team evaluated global cognitive function and specific cognitive domains and regressed

ePWV on cognition at baseline and cognitive change over time. The sample mean ePWV was 12±2m/s is significantly associated with global cognitive dysfunction and specific cognitive domains at baseline and over time. Significant effect modification of ePWV on cognitive function was observed by race, ethnicity, and gender. Black individuals demonstrated the worse effect of elevated ePWV on global cognitive performance, executive function, and executive function change. Hispanic individuals showed a significant effect of ePWV on global cognition. Furthermore, a larger inverse relationship of ePWV with episodic memory change over time was observed in women but not in men. These results suggested an important role of ePWV in cognitive performance and cognitive decline, where some effects were more pronounced among underserved minority participants and women. These findings underscore the importance of preserving healthy vascular function and normal blood pressure in the prevention of age-related cognitive decline and dementia. The newest ePWV analysis, the ePWV measure was significantly associated with WMHV (= 0.11, 95% CI, 0.05 - 0.17), CBI (OR = 1.31, 95% CI, 1.09 - 1.58), and CMB (OR = 1.50, 95% CI, 1.15 - 1.95), but not ePVS. Race and ethnicity modified the association between ePWV and CSVD and significant associations were found in non-Hispanic Black and Hispanic individuals, but not in non-Hispanic White participants. Relationships between ePWV and MRI markers of CSVD reflects the importance of age-related BP dynamics in cerebrovascular injury, with sensitivity to racially and ethnically diverse individuals. The ePWV function may provide a vascular mechanism for deleterious vascular and cognitive outcomes in individuals with CSVD.

Follow-on Funding: University of Miami Miller School of Medicine, $10,578,196.00

Collaborations: The IMAGINE core research team has been collaborating with the UM Center for Cognitive Neuroscience and Aging (CNSA, led by Dr. David Loewenstein-Director and Dr. Rosie Curiel-Co-Director), research team and the 1FL ADRC. The IMAGINE core and CNSA research collaborators met frequently resulting in successful recruitment strategies that increased enrollment. This resulted in 45 subjects being scheduled and enrolled with a final total of 64 subjects. Collaboration with the University of Miami Department of Radiology continued via scheduled bi-weekly meetings assessing MRI imaging quality control (QC) with the study physicist-investigator. The PhD Biomedical Engineering trainee in the IMAGINE study continued to be mentored and trained on QC for the MRI pipeline process and analysis plan of the MRI and ultrasound scans. The research staff were invited to be part of a multi-centered U19 grant with the University of Arizona titled the Precision Aging Network, which is an important project focusing on precision medicine and brain health. It will seek to identify individual patterns of risk and protective factors that predict cognitive functioning in adults ages 50 and older, and to predict how cognition may change across time. The research staff are also involved with the University of California, Davis Campus and are therefore part of a multi-center U19 grant. This project seeks to learn how vascular health and abnormal white matter signals in the brain affect thinking.

Journals: None at the time of reporting.

Patents: None at the time of reporting,

14. **Grant #:** 21A23

Principal Investigator: Mark Kindy, PhD, FAHA

Organization: University of South Florida

Summary: The research team has generated large quantities of the P5 and Fc-P5 for the studies and have screened more compounds that might have beneficial effects. The Research team has tested the compounds in vitro (neuronal cell lines and primary neuronal cultures) to determine the impact of the agonists on neuronal survival and outcomes. Research shows that the GLP-1R agonists can attenuate the expression of both Ab generation and tau phosphorylation in a dose dependent fashion. The research team has completed testing the compounds in several different animals' models of AD. In the three different amyloid precursor protein (APP) transgenic mice (APP/PS-1, 5XAPP, and tau mice), the P5 and P5-Fc both show a dose dependent reduction in Aβ peptide levels and attenuate the deposition of Aβ in the brains of the mice. In the tau transgenic mice, the P5 and P5-Fc both show a reduction in tau phosphorylation and accumulation of neurofibrillary tangles in the brain. The data indicate that the compounds show improvement in the behavioral parameters, reduction in inflammation and oxidative stress. In the APP X db/db mice, the AD pathology is worse in the presence of diabetes. Using the P5 and P5-Fc both showed improved (reduced) diabetic parameters (glucose and A1c) and significantly reduced the AD pathology in the mice. The research team is writing up the results for submission of publications. Additional studies with the mouse model of stroke and TBI have shown both P5 and P5-Fc are effective therapies in the improved outcomes in these models. Researchers have now completed studies in the rats' models to verify the results.

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

Collaborations: This was a continued collaboration with Moffitt Cancer Center. The coinvestigator (CO-I) was Dr. Patsy McDonald in the Cancer Physiology Program at the Moffitt Cancer Center. The CO-I left Moffitt and researchers are completing the studies at the Unviersity of South Florida (USF). The USF research team has both undergraduate and graduate students working on the project, two undergraduate students from the College of Arts and Sciences (CAS) and three graduate students from the Taneja College of Pharmacy (TCOP) masters' graduate program. The research team also includes five PharmD students that are working on the project. In addition, the researchers are collaborating with Drs. Cheryl Kirstein and David Diamond in the Psychology Department at USF. Additional collaborations are with Dr. Derek Duckett at Moffitt, and Dr. Chris Gregg at Utah.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

15. **Grant #:** 21A25

Principal Investigator: Nan Sook Park, PhD, MSW

Organization: University of South Florida

Summary: The goal of the project is to build community capacity for early detection of Alzheimer's disease and related dementias (ADRD) and utilization of services by promoting education of older Asian Americans, their families, and community leaders. This study aimed to promote the knowledge and service utilization of the three largest groups of older Asian Americans in West Florida: Chinese, Korean, and Vietnamese. Based on the dementia care network (DCN) conceptualization, the project has three research objectives and completed tasks are organized by the research objectives. The first research objective was to conduct needs assessments for older Asian Americans (aged 50 and older) 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. The research team completed collecting survey data from the Vietnamese older adults (n=170). Thus, in addition to the 330 surveys that were collected during the last annual report period, a total of 500 surveys were completed (170 Chinese; 160 Korean; and 170 Vietnamese) for the whole project period. The collected surveys were reviewed and validated by the two bilingual research assistants who are fluent in English and in one of the three Asian languages (Chinese, Korean, and Vietnamese). The research assistants entered the data into REDCap and Excel and cross-checked for any errors and discrepancies. The third person validated the data independently. Dr. Park closely worked with Ms. Ruina, (research assistant) to ensure the accuracy in coding and merged data of the three Asian groups. The second research objective was to build community capacity for dementia care by establishing ADRD care network with community leaders and older Asian Americans and their families. The proposal for focus group interviews with Asian American community leaders was approved by the University of South Florida (USF) Institutional Review Board (IRB). The research team completed 24 focus group interviews (n=6 Chinese; n=6 Korean; and n=12 Vietnamese). The focus group interviews were led by Drs. Meng, Park, and Ngo, respectively. The focus group interviews were recorded and transcribed verbatim by research assistants. The transcripts were translated into English and cross-checked for validation. Dr. Nan Park was responsible for overseeing and supervising all efforts. The final research objective was to establish web-based resources for ADRD and relevant services and disseminate the resources.The research team has built local resources and connections, which are integral components of the built-in dementia care network for Asian Americans. Dr. Park has worked closely with the webmaster to set up the website for national and local resources for dementia knowledge and caregiving resources.

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

Collaborations: None at the time of reporting.

Journals: Park NS, Jang Y, Chung S, Chiriboga DA, Haley WE. Relationship of Living and Eating Arrangements to Mental Distress Among Older Korean Immigrants: Gender Difference in the Mediating Role of Loneliness. *Res Aging*. 2024;46(2):153-166. doi:10.1177/01640275231206482.

Patents: None at the time of reporting.

Appendix C: Fiscal Year 2022-2023 Completed Grant Details

Funded Fiscal Year 2019-2020

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
20A05	University of Miami	Hong Jiang, MD, PhD	250,000.00	10/31/2023	No	No	Yes
20A08	University of Florida	Melissa Armstrong, MD, MSC	374,660.00	4/30/2023	No	Yes	Yes
20A16	University of Florida	Sara Burke, PhD	250,000.00	3/31/2023	No	Yes	No
20A21	Mount Sinai Medical Center of Florida	Ranjan Duara, MD	$171,790.00	11/30/2022	No	No	Yes

1. **Grant #:** 20A05

Principal Investigator: Hong Jiang, MD, PhD

Organization: University of Miami

Summary: The research project team undertook a comprehensive endeavor involving the recruitment of study subjects from parental National Institute of Health (NIH) R01 studies. The primary focus of this study was to conduct in-person study visits and gather valuable data from cognitive tests and brain magnetic resonance imaging (MRI) results. This dataset served as the foundation for the analysis to test the hypothesis outlined in the proposed aim. The preliminary analysis included a total of 60 subjects, comprising 19 patients with amnestic Mild Cognitive Impairment (aMCI), 17 patients with pre-MCI, and 24 cognitively normal controls (CN) who were matched by age. The initial investigation revolved around retinal vessel density analysis, which indicated a noticeable trend of decreased retinal vessel density in patients with pre-MCI and aMCI. However, the observed differences in the collected samples did not reach a statistically significant level compared to the control group. With this initial dataset, the research project staff concentrated on exploring the relationships between retinal vessel density and cognition/MRI within the aMCI group. These findings demonstrated significant associations between retinal vessel density and cognitive test results, particularly the Lowenstein-Acebedo Scales for Semantic Interference and Learning (LASSI-L), as well as MRI brain volume measurements. Concurrently, the research project staff continued recruitment efforts from the Department of Neurology, identifying and engaging study patients who met the inclusion/exclusion criteria. As a result, a total of 55 study subjects successfully completed in-person visits, bringing the total number of subjects who participated in the study to 87. In tandem with these recruitment efforts, the research team diligently pursued the objectives outlined in the scope of work supported by the grant, focusing on further analysis of previously acquired data and manuscript preparation. Additionally, an essential study was conducted to assess the impact of different software versions on the measurement of retinal vessel densities using optical coherence tomography angiography (OCTA) in normal subjects. The study involved imaging 32 eyes of 18 healthy subjects using two OCTA devices: the Optovue RTVue and the Zeiss Cirrus. The research project staff identified differences in vessel density measurements between software versions and between devices, marking the first study to reveal that varying software versions and intraretinal layer segmentation methods can affect vessel density measurements. This study was subsequently published in Current Eye Research in March 2021. Another facet of the research involved analyzing previously acquired data to characterize changes in retinal

microvascular density and relationship with cognitive function. This study focused on healthy older individuals without known cognitive impairment who had participated in an eight-week high-speed circuit resistance training program (HSCT). The research project staff discovered that individual responses in retinal vessel density in the superficial vascular plexus (SVD) were linked to improvements in cognition among cognitively normal older individuals after HSCT. The findings from this study were published in Experimental Gerontology in December 2020. Overall, the knowledge acquired from this study provides a better understanding of the early vascular sign in the eye for possible screening of patients with Alzheimer's disease and related dementia.

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

Collaborations: None at the time of reporting.

Journals: Jiang H, Signorile JF, Simms AG, Wang J. Improvement of Retinal Capillary Function After High-Speed Circuit Resistance Training in Healthy Older Adults. J Neuroophthalmol. 2023;43(2):180-184. doi:10.1097/WNo0000000000001679.

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. 2021;46(3):341-349. doi:10.1080/02713683.2020.1801756.

Jiang H, Wang J, Levin BE, et al. Retinal Microvascular Alterations as the Biomarkers for Alzheimer Disease: Are We There Yet?. J Neuroophthalmol. 2021;41(2):251-260. doi:10.1097/WNo0000000000001140.

Fang M, Strand K, Zhang J, et al. Characterization of retinal microvasculature and its relations to cognitive function in older people after circuit resistance training. Exp Gerontol. 2020;142:111114. doi:10.1016/j.exger.2020.111114.

Patents: None at the time of reporting.

2. **Grant #:** 20A08

Principal Investigator: Melissa Armstrong, MD, MSc

Organization: University of Florida

Summary: The focus between July 2022 to June 2023 was on completing analysis, manuscript development, and publication, with four planned publications currently at different stages. The manuscript, "Patient and Caregiver Communication Preferences for Receiving a Dementia Diagnosis: An Interview Study," is under review at PEC (Patient Education and Counseling) Innovations. It reflects results of patient and caregiver interviews. Patients and caregivers preferred for clinicians to communicate the dementia diagnosis clearly and positively, meet information needs, discuss support resources, prepare for continued care, and communicate to establish and maintain relationships. Patients and caregivers felt clinicians should tailor communication based on individual preferences and backgrounds to best meet both groups' needs, including tailoring communication to preferences for when, how much, or which information is given. While there was a previously published manuscript, another manuscript,

"Barriers and Best Practices in Disclosing a Dementia Diagnosis: A Clinician Interview Study" was published December 2022 in Health Services Insight. In this manuscript, clinician-reported barriers to giving a dementia diagnosis fit three categories: patient and caregiver-related barriers, clinician-related barriers, and barriers related to the triadic interaction. Patient and caregiver-related barriers included lack of social support, misunderstanding the diagnosis, and denial. Clinician barriers included difficulty giving bad news, difficulty communicating uncertainty, and lack of time. Triadic interaction barriers included challenges meeting multiple goals or needs and family requests for non-disclosure. Recommendations for best practice included for clinicians to foster relationships, educate patients and family, and take a family-centered approach. Clinicians described recommendations for fostering relationships such as using empathic communication and developing and maintaining connection. Educating patients and families included tailoring communication, explaining how the diagnosis was reached, and following up. Family approaches included meeting with family members prior to delivering the diagnosis and involving the caregiver in the discussion. The manuscript, titled "Best Practices for Communicating a Diagnosis of Dementia: Results of a Multi-Stakeholder Modified Delphi Consensus Process" was accepted for publication in Neurology: Clinical Practice in September 2023 but is not yet in press. This manuscript summarized results from the working group which convened from May 2022 to January 2023. Seven best practice statements achieved consensus after a maximum of three rounds of voting: 1. Clinicians must show compassion and empathy when delivering a diagnosis of dementia (Level A). During dementia diagnosis disclosure, clinicians should: 2. ask regarding diagnosis preferences, 3. instill realistic hope, 4. provide practical strategies, 5. provide education and connections to high-quality resources, 6. connect caregivers to support resources, and 7. provide written summaries of the diagnoses, plan, and relevant resources (each Level B). Clinicians need to customize discussion of a dementia diagnosis for individual patients and their caregivers. These seven best practices provide a diagnosis communication framework that can be implemented across varied clinical settings. The fourth in-process manuscript reflects the results of a scoping review; the literature search for this review needing updating prior to submission for publication. Apart from updating the review, the study has completed data analysis and was closed with the University of Florida (UF) Institutional Review Board (IRB).

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

Collaborations: University of Florida, University of Miami, and Florida Atlantic University contributed to manuscript development and study closure procedure. These institutions submitted the necessary final forms before study closure with Florida Department of Health and have provided edits/comments on the four manuscripts in development.

Journals: Wollney EN, Armstrong MJ, Bedenfield N, et al. Barriers and Best Practices in Disclosing a Dementia Diagnosis: A Clinician Interview Study. *Health Serv Insights*. 2022;15:11786329221141829. Published 2022 Dec 5. doi:10.1177/11786329221141829.

Patents: None at the time of reporting.

3. **Grant #:** 20A14

Principal Investigator: Claes Wahlestedt, MD, PhD

Organization: University of Miami

Summary: Considering the recent shortcomings of Alzheimer's disease (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 histone deacetylases (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. Using validated tools, the preliminary data unexpectedly suggested that interrupting HDAC8 signaling could potentially aggravate AD-like pathogenesis. The studies conducted with funds from this grant in this reporting period aimed to further test the hypothesis whether a small molecule compound that either increases HDAC8 activity or inhibits HDAC class I while sparing HDAC8 could be beneficial for AD. The research staff investigated the effects of the small molecule epigenetic compound CTI-701 on AD pathways. Transcriptomic profiling from AD mouse models that were treated with and without CTI-701 revealed that, in the brain, the drug significantly affected genes in networks that are highly relevant to neuroprotection and metabolic regulation compared to controls. Because Alzheimer's disease is a complex polygenic disease, it is encouraging to see that CTI-701 has a multifactorial effect in the brain. Interestingly, the research staff observed that, in the brain, CTI-701 significantly affected genes involved in neuroinflammation differently in males versus females in a relevant AD mouse model. This is highly relevant to Alzheimer's because inflammation has been found to play a major role in the brain pathology of patients. Impact to Floridians: In Florida, approximately half a million people currently suffer from AD. Data from the proposed work can validate whether a selective small molecule with an epigenetic mode of action can lead to a novel therapeutic strategy for AD while avoiding undesirable side effects. This project has the potential to yield a small epigenetic molecule suitable for AD treatment 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.

4. **Grant #:** 20A16

Principal Investigator: Sara Burke, PhD

Organization: University of Florida

Summary: Research staff have made considerable progress on multiple fronts in order to test whether a cyclic ketogenic can confer resilience to age-related cognitive decline and

Alzheimer's disease-related Tau pathology. This research progress has included completion of the cognitive assessment of adeno-associated viral vector (AAV)-mediated Tau overexpression on Paired Associated Learning (PAL) in middle-aged rats, and the initiation of assessing whether a cyclic ketogenic diet in aged and young female rats improves brain biochemistry and metabolism. Progress has been made on the AAV-mediated Tau Overexpression in the Transentorhinal cortex. Intracellular inclusions comprised of tau proteins are among the earliest pathological features observed in Alzheimer's disease. Although transgenic animal models have been useful in understanding Alzheimer's disease-related tau pathology in animals that have mutations of this gene, it remains unclear how tau inclusions forming from the wildtype variant of this protein that occurring with aging in the transentorhinal cortex affects cognition. The research team evaluated the behavioral effects of human wildtype tau overexpression in area 35 of the perirhinal cortex, which is homologous to the human transentorhinal cortex and among the first brain areas to show early tau pathology (Braak et al., 1993). Male (n=20) and female (n=20) F344/BN rats (aged six to eight months) received intercranial injections of adeno-associated viral vector containing either human wildtype tau (AAV-hWTtau), eGFP alone (AAV-eGFP), tdTomato alone (AAV-tdTomato), or a floxed eGFP (pCAGFLEX-EGFP-WPRE) that served as a surgical control so that virus was injected but no protein would be expressed. All viruses were place in three injection sites along the longitudinal extent of the perirhinal cortex area 35. After a two-week recovery period, rats were behaviorally assessed on the paired associates learning (PAL) task in touchscreen operant chambers (Smith et al., 2022). The PAL task was adapted for use in rodents from the human version that is used clinically (Robbins et al., 1994; Robbins et al., 1997). The PAL task is perirhinal cortical and hippocampal dependent (Talpos et al., 2009). The investigators therefore predicted that it would be a sensitive measure of behavioral dysfunction that arises following the development of early tau pathology. After completion of PAL testing on three different variants of the task with different levels of difficulty, spatial reference memory was assessed on the Morris watermaze (Morris et al., 1982). Two weeks following cognitive testing, animals were transcardially perfused, and brains were processed for immunohistochemistry to assess tau, eGFP, or tdTomato expression within the perirhinal cortex and associated structures. Although significant tau expression and hyperphosphorylation was evident, PAL performance was not significantly different between the AAV-hWTtau and the three control groups on any variants of the task. Moreover, Morris watermaze performance also did not significantly vary between the different groups. These data suggest that tau overexpression does not lead to behavioral impairment. It is therefore likely that tau protein by itself is not responsible for the cognitive impairments associated with Alzheimer's disease. The previous data that have been collected by study staff showing beneficial effects of a cyclic ketogenic diet have all been collected from male rats. This is because the Fischer 344 x Brown Norway hybrid strain of rats that the research staff established the cyclic ketogenic diet model in did not have aged female animals available until recently. The research staff were able to acquire aged females in December have now begun this work in females.

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

Collaborations: Research staff have begun a new collaboration with Drs. Matthew Gentry and Ramon Sun in the University of Florida Department of biochemistry. Both are experts in glucose metabolism and Dr. Sun is a world-renowned expert in spatial metabolomics. Dr. Sun is currently processing brain tissue from animals that were part of these studies, and the researchers are excited to use these data for future grant submissions.

Journals: None at the time of reporting.

Patents: None at the time of reporting.

5. **Grant #:** 20A19

Principal Investigator: Noam Alperin,

Organization: University of Miami

Summary: Despite the pandemic, the support from Florida Departmet of Health (FDOH) enabled the researchers to achieve two scientific breakthroughs. Further analysis of data collected during a previous award, revealed that at the early preclinical stage of Alzheimer's disease (AD) i.e., pre-amnestic mild cognitive impairment (aMCI), total cerebral blood flow (tCBF) is reduced compared to age-matched healthy subjects, while there was no loss in the volumes of AD-prone brain regions. Researchers further found that tCBF is more strongly associated with cognitive performance than volumes of AD-prone brain regions. These findings not only strengthen the power of tCBF as a key bio-marker for early aMCI, but also implies that interventions to improve blood supply to the brain my slow down progression to AD. The findings of lower tCBF while volumes of AD-prone regions are still normative implies that reduction in CBF occurs before onset of accelerated tissue loss in AD. This important information will help elucidate the role of CBF in the progression from elevated amyloid beta loads to tissue loss. This work was published in the journal Alzheimer's disease in 2023 and is titled:" Early Amnestic Mild Cognitive Impairment Is Associated with Reduced Total Cerebral Blood Flow with no Brain Tissue Loss". The article concludes that "Reduced tCBF is a sensitive biomarker of early aMCI that likely precede brain tissue loss." A second scientific breakthrough is the advancement of the understanding of the link between poor sleep and increased risk for AD. This work was just published in September, in the journal sleep research. Clearance of brain toxins occurs during sleep, although the mechanism remains unknown. Previous studies implied that the intracranial aqueductal cerebrospinal fluid (CSF) oscillations are involved, but no mechanism was suggested. This study focuses on the cranio-spinal CSF oscillation and the factors that modulate this flow. The research team proposed a mechanism where increased cranio-spinal CSF movements enhance CSF-to-blood metabolic waste clearance through the spinal CSF re-absorption sites. Researchers quantified the effect of respiration on the cranio-spinal CSF oscillations. Maximal CSF volume displaced from the cranium to the spinal canal during each respiration and cardiac cycle were derived as measures of cranio-spinal CSF mixing level. Transition from normal to slow and abdominal breathing resulted in a significant increase in the maximal displaced CSF volume. The researchers demonstrated that a breathing pattern during slow wave sleep maximizes the movement of CSF between the cranium and spinal canal, which explains enhanced CSF-to-blood toxins clearance during deep and poor clearance during disrupted sleep. A world leader sleep expert, Dr. Lucey, wrote "I just read your recent paper and wanted to email my congrats. I think it is great work and an innovative approach to study how breathing affects arterial, venous, and CSF flow. As you note, there is substantial evidence that sleep affects clearance in the brain but the mechanism (or mechanisms) is unclear due at least in part to difficulty measuring dynamic changes in fluid flow

during wake and sleep. I think your approach elegantly provided new information about the potential mechanism, although with the limitations you noted in the paper."

Follow-on Funding: Grant Title: Do craniospinal CSF oscillations play a role in the Clearance of Toxins from the Brain?; Federal Agency/Institute: National Institutes of Health; Principal Investigator: Alperin N; Grant Term: 4/1/2024-3/31/2026; Submisison Date: 7/10/2023; Grant Category: R21; Total Funds Requested: $419,805.00; Status:Pending.

Collaborations: None at the time of reporting.

Journals: Liu C, Lee SH, Loewenstein DA, et al. Early Amnestic Mild Cognitive Impairment Is Associated with Reduced Total Cerebral Blood Flow with no Brain Tissue Loss. *J Alzheimers Dis*. 2023;91(4):1313-1322. doi:10.3233/JAD-220734.

Burman R, Alperin N. CSF-to-blood toxins clearance is modulated by breathing through cranio-spinal CSF oscillation. *J Sleep Res*. Published online September 21, 2023. doi:10.1111/jsr.14029.

Patents: None at the time of reporting.

6. **Grant #:** 20A21

Principal Investigator: Ranjan Duara, MD

Organization: Mount Sinai Medical Center of Florida

Summary: To diagnose Alzheimer's Disease (AD), doctors conduct tests to assess memory and thinking, judge functional abilities, and identify behavior changes. In addition, expensive brain imaging procedures are often ordered, including magnetic resonance imaging (MRI) scans to check for evidence of brain atrophy, and polyehtylene terephthalate (PET) scans to determine the level in the brain of a hallmark early protein associated with AD: Beta Amyloid . This protein and other biomarkers associated with AD can also be measured in cerebrospinal fluid obtained from a lumbar puncture. However, a lumbar puncture is too invasive for wide acceptance. The purpose of this grant was to validate biomarkers from relatively inexpensive blood tests that can detect the presence of AD pathology in the brain at an early stage, even before overt memory impairment. In this study, the resources of the National Institute on Aging (NIA)-funded 1Florida Alzheimer's Disease Research Center (1FL ADRC) at Mount Sinai Medical Center were leveraged by collecting blood samples from 127 participants who came for annual follow-up clinical and neuropsychological assessment. These participants also had MRI scans and Amyloid PET scans to detect the level of amyloid in the brain, as part of the participation in the 1Florida ADRC. The blood samples were analyzed for plasma biomarkers by the University of Florida using technology from Quanterix, a leader in the field. Blood-based biomarkers were also obtained from additional participants in the 1FL ADRC using other funding sources. The data showed that one of the blood-based biomarkers, neurofilament light (NfL), was significantly elevated in people with Alzheimer's Disease (AD) and frontotemporal lobe degeneration (FTLD) compared to subjects who were cognitively normal. However, the best predictors of elevated amyloid in the brain were biomarkers known as p-tau181 and p-tau217. These blood-based biomarkers performed equally well in detecting brain amyloid in participants of Hispanic (57% of

the cohort) and non-Hispanic ethnicity, which is a contribution to the existing research done in populations with limited ethnic diversity. This study adds to the growing evidence that blood-based biomarkers can be used in a clinical setting to identify patients who have elevated amyloid in the brain. The publications from this study will support the five-year renewal application to NIA for the 1Florida ADRC which is due on June 14, 2024. Early detection and intervention will become increasingly important as disease-modifying drugs such as LEQEMBI become more accessible. In addition, earlier and more accurate diagnosis of AD will also allow for timely intervention for social, legal, and financial issues and the education of the patient and caregiver.

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

Collaborations: The Principal Investigators (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 students (University of Miami Coral Gables Campus) have been involved with this research project. Along with one Summer Undergraduate Research Fellow (SURF) from Barry University chemistry program also worked on this project.

Journals: Asken BM, Wang WE, McFarland K, et al. Plasma Alzheimer's biomarkers and brain amyloid in Hispanic and non-Hispanic older adults. *Alzheimers Dement*. Published online September 6, 2023. doi:10.1002/alz.13456.

Curiel Cid RE, Ortega A, Crocco EA, et al. Semantic intrusion errors are associated with plasma Ptau-181 among persons with amnestic mild cognitive impairment who are amyloid positive. *Front Neurol*. 2023;14:1179205. Published 2023 Aug 4. doi:10.3389/fneur.2023.1179205.

Barker W, Quinonez C, Greig MT, et al. Utility of Plasma Neurofilament Light in the 1Florida Alzheimer's Disease Research Center (ADRC). *J Alzheimers Dis*. 2021;79(1):59-70. doi:10.3233/JAD-200901.

Patents: None at the time of reporting.

Appendix C: Fiscal Year 2022-2023 Completed Grant Details

Funded Fiscal Year 2018-2019

Grant #	Institution	Principal Investigator	Award Amount	End Date	Patents	Follow-on Funding	Publications
9AZ02	Florida Atlantic University	Henriette van Praag, PhD	$250,000.00	2/28/2023	No	No	No

1. Grant #: 9AZ02

Principal Investigator: Henriette van Praag, PhD

Organization: Florida Atlantic University

Summary: 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. Indeed, these researchers were the first to show that running increases the production of new neurons in the hippocampus, a region important for learning and memory. Since this discovery, the research team 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. These studies indicate that myokines, can increase neural stem cell differentiation, and may be important for improvements in memory function in mice and humans. Researchers propose 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 researchers are studying the effects of voluntary wheel running, a compound that activates muscle energy metabolism, the activated protein kinase (AMPK) agonist 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), and the novel myokine Cathepsin B, on memory function in amyloid precursor protein's (APP's) swe/PS19 transgenic mice. The researchers are evaluating adult hippocampal neurogenesis and synaptic plasticity after these manipulations. The mouse behavioral experiments have been completed and are being analyzed. In particular, the researchers have evaluated spatial memory function. In addition, the research team have prepared viral vectors and performed stereotaxic surgeries to target newly born neurons in the hippocampus of AD mice housed under control and running conditions and are in the process of analyzing the fine morphology of adult-born neurons. The research team will also assay Aβ and tau levels in the hippocampi and cortices of these subjects. Researchers also aim to discover novel myokines that may aid brain function. 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: None at the time of reporting.

Patents: None at the time of reporting.

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[10] Ibid.

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MCI due to Alzheimer's disease and those with biomarker-confirmed preclinical Alzheimer's disease) will be even higher than any estimates presented in the current report." 2023 Alzheimer's disease facts and figures. doi:10.1002/alz.13016, 23.

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[15] 2023 Alzheimer's disease facts and figures. doi:10.1002/alz.13016.

[16] Ibid.

[17] Alzheimer's Association and Centers for Disease Control and Prevention. Healthy Brain Initiative, State and Local Public Health Partnerships to Address Dementia: The 2018-2023 Road Map. Alzheimer's Association; 2018. https://www.cdc.gov/aging/pdf/2018-2023-Road-Map-508.pdf; Advancing Early Detection, Alzheimer's Disease and Healthy Aging, CDC, https://www.cdc.gov/aging/healthybrain/issue-maps/early-detection.html (Last Accessed Feb 12, 2024).

[18] Advancing Early Detection, https://www.cdc.gov/aging/healthybrain/issue-maps/early-detection.html; Taylor CA, Bouldin E, McGuire L (2018). Subjective cognitive decline among adults ≥ 45 years—49 states, Puerto Rico, and the District of Columbia, 2015-2016. *MMWR Morb Mortal Wkly Rep*. 2018;67:753-757.

[19] Ibid.

[20] Fla. Stat. 381.82,2(c) (2014).

[21] NIH Budget Request, National Institutes of Health, Overview of FY 2024 Executive Summary.pdf (nih.gov).

[22] "The data in these files are "frozen" annually to ensure the reporting files produce consistent and meaningful results. It is imperative that corrections to the data occur through the Grant Re-assign function in eRA Commons before these files are frozen to ensure the accuracy of NIH's FY2023 reports. (…) During the current fiscal year, changes that occur before each Friday evening will appear on RePORTER and Awards by Location and Organization websites on the following Monday if the awards have passed their budget start date as noted in the section above. In all cases, the listings in Commons should be considered official for FY2023 until the deadline for correction. The official frozen awards data are expected to be released through the Awards by Location and Organization page in December," Review of the Accuracy of Grants Information for Fiscal Year 2023. Office of The Director, National Institutes of Health. September 26, 2023. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-23-168.html.

[23] Office of The Director, National Institutes of Health. September 26, 2023. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-23-168.html.

[24] Ibid.

[25] "Consortium: A consortium should involve partnerships to be developed among investigators across the state of Florida, with the award made to the lead organization. The lead organization of the consortium must perform a substantive role in conducting the planned research including providing oversight of all scientific, programmatic, financial, and administrative matters related to the grant. The collaborating organizations must have well-defined roles that contribute to the common scientifically rigorous research goals, and include sound background information, hypotheses, protocols, and promising practices that address clearly one or more areas of research interest. A letter of commitment from all collaborating organizations is required," Ed and Ethel Moore Alzheimer's Disease Research Program Funding Opportunity Announcement, FY 2023-2024. https://www.floridahealth.gov/provider-and-partner-resources/research/funding-opportunity-announcements/ALZFinalFOAFY23-24_6.15.2023-NoHighlights-06232023.pdf.

[26] "A comprehensive approach to patient care that results in an improvement in patients' lives will be an effective way to decrease the costs and address this global health burden. The availability of accurate disease data is crucial to determine the risk factors of the disease and identify targets for treatment and prevention. Disease registries are considered one of the most cost-effective ways of collecting patient information and longitudinal follow-up data that can be used for research purposes as well as clinical observations," Heikal SA, Salama M, Richard Y, Moustafa AA, & Lawlor B, (2022). The Impact of Disease Registries on Advancing Knowledge and Understanding of Dementia Globally. *Frontiers in aging neuroscience*, 14, 774005. doi:10.3389/fnagi.2022.774005; Gliklich RE, Michelle B, Leavy MPH, Daniel Levy J, Karl MBA, Daniel PMP, et al. (2012). Research from the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network Effective Health Care Program Registry of Patient Registries (RoPR) Policies and Procedures. https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registry-of-patient-registries_research-2012-2_1.pdf; "Cancer registries, in particular, are regulated, linked, and share nomenclature across disease types, stages of diagnosis, and treatments (NAACCR, 2020), expanding the possibilities of innovative cancer prevention and control approaches to address the most common and rarer

cancers competently, powerfully, cost-effectively, and compassionately across the continuum of cancer care," Miller MC, Bayakly R, Schreurs BG, Flicker KJ, Adams SA, Ingram LA, Hardin JW, Lohman M, Ford ME, McCollum Q, McCrary-Quarles A, Ariyo O, Levkoff SE and Friedman DB (2023) Highlighting the value of Alzheimer's disease-focused registries: lessons learned from cancer surveillance. Front. Aging 4:1179275. doi:10.3389/fragi.2023.1179275; Krysinska, K., Sachdev, P. S., Breitner, J., Kivipelto, M., Kukull, W., & Brodaty, H. (2017). Dementia registries around the globe and their applications: A systematic review. Alzheimer's & dementia : the journal of the Alzheimer's Association, 13(9), 1031–1047. doi:10.1016/j.jalz.2017.04.005; Alzheimer's Association Announces National Effort to Collect "Real World" Data on Newly-Approved Treatments, Alzheimer's Association (Nov 9, 2021) https://www.alz.org/news/2021/alzheimers-association-announces-national-effort.

[27] Ibid et al.

[28] 2023 Alzheimer's disease facts and figures. doi:10.1002/alz.13016, 52.