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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Melissa Murray	Mayo Clinic Jacksonville	Clinicopathologic and genetic differences of neurodegenerative health disparities in the State of Florida brain bank	Alzheimer's disease is a devastating neurologic disorder that is estimated to affect 5.3 million Americans. Much progress has been made toward characterizing the changes in the brain at the clinical level, tissue level, and molecular level. There is unfortunately a skewed representation of information about Alzheimer's disease in non- Hispanic White Americans. Moreover, the frequency of other common neurologic disorders in Hispanic and Black Americans is poorly characterized. Our overall goal is to examine similarities and differences in brain diseases, cognitive decline, and genetics across these three ethnoracial backgrounds. Currently, brain autopsies are the only way to confirm from which brain disease an individual suffered. By leveraging one of the State of Florida's most valuable resources, the Alzheimer's Disease Initiative brain bank; we plan to specifically investigate Alzheimer's and other brain diseases (e.g., Lewy body disease) in Floridians across ethnoracial groups. Alterations in brain proteins, amyloid-β and tau, occur throughout a patient's disease course. These proteins form in characteristic patterns, but only around 20% of Alzheimer's disease brains have no other co-existing pathologies found. Vascular diseases are observed to be more common in black Americans when compared to Hispanic and non-Hispanic White Americans. Based on this knowledge, our first goal will be to test the hypothesis that coexisting pathologies (e.g., Alzheimer's and vascular disease) will be more common in Black Americans than Hispanic and non-Hispanic White Americans. The Department of Elder Affairs has continued to support a state-wide brain bank program that has enabled us to characterize each individual, but with restricted funding we have had to take an economic approach. Thus, the Ed and Ethel Moore Alzheimer's Disease Research Program will play a critical role in enabling us to enhance the Florida brain bank to allow us and others to investigate critical questions that directly inform our aging population. To facilitate translation of our findings to practicing neurologists, we will database useful information regarding clinical course – age of onset, early symptoms, disease duration, and rate of cognitive decline. We will employ advanced digital pathology methods that will enable us to both visualize and quantify brain pathology, with a particular focus on tau pathology. Tau pathology can also be found to be associated with aging, and within a molecularly defined group of diseases called tauopathies – both of which have been shown to have a clinical impact on sufferers. Ethnoracial differences in age-related tauopathies are currently unknown. Moreover, ethnoracial genetic differences in genes associated with dementia have not been examined. Using a cost-effective method to detail genetic differences will further enrich characterization of Alzheimer's Disease Initiative brain bank cases and provide valuable information for the current and future projects. In summary, we will be well-positioned to answer critical questions on frequency and variations in Alzheimer's disease and other brain diseases in an ethnoracially diverse autopsied series of Floridians through the proposed systematic clinical, neuropathologic, and genetic characterizations.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
James Galvin	Florida Atlantic University	Caring For You (C4U): A Novel Intervention to Improve Caregiver and Patient Outcomes and Quality of Life	Alzheimer's disease (AD) and related disorders affects over 5 million Americans and over 500,000 Floridians. Each person with dementia (PWD) is estimated to have 2.5 family caregivers (FCG). In Florida, these nearly 1.2 million FCGs are estimated to provide millions of hours of care annually for a total cost valued at over $14 billion. Little attention has been placed on the role of the family unit on dementia outcomes and the impact of cultural beliefs and sociodemographic factors (age, gender, education, race/ethnicity) of FCGs on their understanding of the signs, symptoms, causes, or management of AD and their disease experiences. AD caregiving is a biomedical challenge - as a direct result of caregiving, FCGs are at increased risk for health problems such as heart disease, headaches, digestive problems, disturbed sleep, reduced immunological function, and inflammatory biomarker changes. These biomedical challenges potentially limit the FCGs ability to care for themselves and as a result affect the care of the PWD, often with deleterious and expensive consequences (poor health outcomes, hospital admissions, transition to long-term care). We propose to test a novel, bilingual intervention, Caring for You (C4U) [in Spanish "Cuidandote""] in a clinical trial of 150 PWD/FCG dyads compared with a "usual care" control group (i.e., printed information,support groups). C4U was developed by an interdisciplinary team of physicians, nurses, sociologists, psychologists, and gerontologists with each of its components initially tested and validated separately: (a) Personalized care consultations; (b) Family-centered, problem-solving skills training; (c) Strategies for FCG self-care, health promotion and stress-reduction; and (d) Facilitated FCG assessment of emergent AD symptoms and response to therapy. To understand potential cross-cultural differences, we also examine the impact of health literacy, acculturation, and familism on outcomes. We propose 3 Specific Aims to test our hypotheses: 1) Test ability of C4U to improve FCG care management skills; 2) Evaluate ability of C4U to improve FCG self-reported and biomarker health outcomes; and 3) Determine ability of C4U to improve PWD health resource utilization and medicoeconomic outcomes. C4U has the potential to exert sustained influence on the approach to AD in Florida. This novel multicomponent program is derived from the best practices of effective and culturally-tailored caregiver intervention programs. It is uniquely designed to enable FCGs to address the complex challenges they are likely to encounter across the caregiving trajectory. It will demonstrate that providing engaged FCGs with the necessary symptom assessing and problem-solving skills for appropriate AD management and demonstration of learning and behavioral change in the home setting will lead to improved clinical care of PWDs, improved health outcomes for FCGs, and reduced healthcare costs. Furthermore, C4U will validate a cross-cultural approach to dementia care that can be generalized for broad implementation. This study has direct implications for clinical practice and health policy meeting the goals of the National Alzheimer's Project Act to optimize care quality and expand support for PWDs and FCGs while also meeting the Center for Medicare and Medicaid Services "Triple Aim" of improving patient health, improving patient care, and reducing healthcare costs.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
David Loewenstein	University of Miami	Post-doctoral Fellowship Training Program in Cross-Cultural Neuropsychological Assessment and Development of Novel Tools to Assess Preclinical Alzheimer's Disease	There is a pressing need to train promising researchers to study more innovative ways of assessing and diagnosing persons in the earliest stages of disease (AD). Early diagnosis paves the way for increasingly more targeted treatment interventions. This application presents an unprecedented opportunity for post- doctoral neuropsychology fellowship training to a) study the earliest Preclinical manifestations of AD; b) participate in the development and implementation of novel measures to assess PreClinical AD; c) learn to clinically evaluate different ethnic and cultural groups for early stage mild-cognitive impairment; d) learn how to interpret and to conduct research relating cognitive and functional test findings to biological measures of the brain and e) learn to publish papers and prepare NIH funded applications for further extramural grant support.The primary mentor for the fellow would be Dr. David Loewenstein, PhD, ABPP, a board certified neuropsychologist, Director of the Division of Neuropsychology and Professor of Psychiatry and Behavioral Sciences at the Miller School of Medicine at the University of Miami Miller School of Medicine. Dr. Loewenstein is currently Principal Investigator (PI) of a five year R01 studying novel cognitive paradigms for the prediction of cognitive decline in the elderly. He is also co-leader of the Clinical Core and Scientific Project Director of the newly funded Alzheimer's Disease Research Center (ADRC) located at Mount Sinai Medical Center. that relates novel cognitive and brain biomarkers to cognitive decline in Preclinical AD in Hispanic and Non-Hispanic populations. Dr. Loewenstein would be assisted by co-mentors Dr. Sara Czaja, PhD (University of Miami); an internationally recognized expert in functional assessment in the elderly, Dr. Rosie Curiel, (University of Miami) who has a focus on cross-cultural neuropsychological assessment and Dr. Maria Greig (Mount Sinai Medical Center) who has expertise in amyloid PET neuroimaging. Interaction with these mentors would provide an unprecedented opportunity for a post-doctoral fellow to gain extensive research and clinical diagnostic experience.We believe that the proposed fellowship will help cultivate fresh talent into the critical area of early diagnosis of older adults representing different cross-cultural groups, provide excellent academic mentorship by distinguished investigators and clinicians and prepare the individual for a successful career in clinical patient oriented research.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Sara Czaja	University of Miami	A Non-Pharmalogical Intervention for Patients with Alzheimer's Disease and Family Caregivers	Alzheimer's disease (AD) is a devastating illness affecting patients, family members and society. Family members represent the largest source of care and support for Alzheimer's patients. While they provide a great service to their family and their loved one many do so at considerable cost. Thus, there is a need to identify interventions that decrease the cognitive and functional/behavioral manifestations of AD in the patient and the negative consequences experienced by family caregivers. Recent evidence suggests that non- pharmacological intervention approaches can be beneficial to both the caregiver and patient and that caregivers can successfully deliver these interventions to patients. To date, most intervention programs have exclusively focused on the caregiver or the patient despite the reciprocal relationship between them. Also, most caregiver programs have targeted caregivers of patients in the moderate to severe stages of the illness. Further, cognitive interventions for AD patients have been dependent on facility based training approaches, which limit their cost effectiveness and feasibility. This proposed study will develop and test the efficacy and feasibility of a dyadic-based intervention program (DT), delivered through state-of-the art computer tablet technology, that will focus on both the caregiver and the AD patient and combine an evidenced-based caregiver intervention component and an evidenced-based cognitive/functional training component for the patient. The program will be tailored to the needs of the caregiver and emphasize issues important to caregivers in the earlier stages of caregiving but also targets issues across the caregiving trajectory to help prepare the caregiver for the caregiver role at the later stages of the disease. It will also be culturally tailored. The cognitive/functional training will be targeted to the specific needs of the AD patient. The DT program will be designed to promote a collaborative care pattern and positive interactions between the patient and the caregiver and enhance outcomes for both. Given that this is a developmental and feasibility trial, the program will be compared to a control condition that combines standard caregiver educational material and standard mental stimulation exercises for patient. The study sample will include Hispanic, and White Caucasian caregivers of mild AD patients and the patient. Measures will include indices of patient cognitive and functional status, quality of life and distress, and caregiver outcomes such as quality of life, distress, and caregiving efficacy. We will also gather information on ethnic differences in response to the intervention and estimates of cost effectiveness. The DT intervention is highly innovative given the focus on both the caregiver and the AD patient, the use of state-of-the-art technology for intervention delivery, the inclusion of the caregiver as a therapy extender and cultural tailoring of the program. The program builds on existing research in caregiving (e.g., evidenced-based REACH II intervention program, NIH funded Caring for the Caregiver Network study (S. Czaja PI)), functional assessment and cognitive rehabilitation strategies developed at the University of Miami Center on Aging and the protocols for technology-based interventions developed by the NIH funded Center for Research and Aging and Technology Enhancement (CREATE) Center (S. Czaja, PI).

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Linda Cottler	University of Florida	Linking Older Adults from the Community in Florida to Memory Screening and Related Health Research	Prevention strategies and effective treatments for Alzheimer's disease (AD) are seriously needed in Florida, an epicenter of AD in the US, with 500,000+ AD patients and 3 million 65+ year olds. While Hispanics and African Americans have a high rate of late onset AD, and represent 40% of Floridians, they are seriously underrepresented in research related to AD and other memory disorders (MD). Lack of awareness of these disorders or research studies focused on them could be associated with delayed screening and low participation, resulting in poor prognosis and irrelevant treatments. To improve health and give more people a voice in research, especially African Americans and Spanish Speakers, new methodologies are needed. Our project will raise awareness for AD in the community and provide ethnically diverse community members an unprecedented opportunity to participate in innovative, culturally relevant screening, treatment efforts and research initiatives. We will do this by engaging community members through our person-centered, evidence based outreach model, HealthStreet, now based in Gainesville and Jacksonville. This model would be expanded to three more regions of Florida with the highest rates of AD mortality: Northwest (7 counties), Northcentral (6 counties) and South Florida (4 counties). The backbone of HealthStreet is Community Health Workers (CHW) from the local/regional community who engage people where they live, work and recreate. CHWs, who now assess community members for health needs and concerns in order to link them to relevant medical and social services and opportunities to participate in health research, will expand their repertoire to assess for mild cognitive impairment (MCI) using a reliable tool. Through this effort, they will facilitate bidirectional communication between the community and scientists, which will reduce disparities, increase knowledge of AD and build trust in the research enterprise. The HealthStreet Registry would expand with a focused AD Registry, protected by the highest standards for privacy, to facilitate a match between community members interested in AD research and scientists involved in developing AD diagnostics and therapeutics. Our project complements statewide efforts of UF, Mount Sinai Medical Center, Florida Memory Clinics and many other institutions, and the new Florida Alzheimer's Disease Research Center (ADRC) that is involved in improving early diagnosis and developing innovative culturally relevant research. Specifically, the project will launch the innovative, statewide community focused outreach program for underrepresented, diverse populations. Approximately 3,600 older adults will be assessed through CHWs for MCI, social determinants of health, medical history, perceptions of and trust in AD research, and family history of AD. We then will navigate 360 65+ year olds with mild cognitive impairment, in the new Florida AD Registry, to research across Florida. Our project would eventually facilitate a link to the National AD Patient Powered Research Network. Our multidisciplinary team spanning epidemiology, neurology, psychology, medicine and the Community Advisory Board will use methods that reduce barriers and increase trust in the research enterprise. With ongoing person-centered contact, we will track our efforts to increase AD knowledge, trust in research, recruitment, enrollment and retention in AD research that improves population health.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
John Fryer	Mayo Clinic Jacksonville	Clusterin prevention of Alzheimer pathology	Alzheimer's disease (AD) is the most common cause of dementia and is pathologically characterized by extracellular plaques formed by the deposition of amyloid-β (Aβ) peptide and intracellular tangles comprised of hyperphosphorylated forms of the tau protein. Clusterin (CLU, aka ApoJ) binds to the Aβ peptide both in vitro and in vivo and multiple large-scale genome wide association studies have demonstrated a highly significant association of CLU with human AD cases (CLU is currently the third ranked gene on AlzGene.org). The mechanism underlying these effects or whether CLU genotype alters pathology in humans is currently unknown, but determining precisely how CLU influences AD risk is critical and will likely lead to new therapies. CLU has chaperone properties and can bind to diverse types of protein deposits that adopt a misfolded or amyloid conformation. We have found that CLU protein levels are significantly elevated in AD cases that have abundant amyloid and tau pathology. We have found that CLU can inhibit Aβ fibril formation in vitro and in vivo using the APP/PS1 mouse model of amyloidosis on a Clu+/- background (i.e. a 50% reduction in CLU protein) results in a significant increase in the amount of parenchymal amyloid plaques, gliosis, and neuroinflammation. Interestingly, we have also found that CLU is substantially elevated in frontotemporal dementia cases with abundant tau pathology (but no amyloid) as well as mouse models of tauopathy (Tg4510 mice). We have found that CLU can directly bind to tau and can substantially inhibit tau fibril formation in vitro. These data suggest that CLU could play a central role in the two major pathologies associated with AD (Aβ and tau), consistent with the proposed chaperone function of CLU. In this proposal, we will use mouse models that develop amyloid or tau pathology and directly manipulate the levels of CLU to determine the effect using multiple readouts including behavior, histology, biochemistry, and inflammation. These studies will allow us to determine how CLU levels impact the two main pathologies of AD and may indicate that CLU is a prime therapeutic target in the treatment of this devastating disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Meredith Wicklund	University of Florida	Consortium for Diagnostic Algorithm with Novel Markers in Early Alzheimer's Disease	There is increasing recognition that the onset of Alzheimer's disease (AD) occurs many years before the emergence of clinical symptoms and a formal diagnosis. Early pharmacological and non-pharmacological interventions are likely to be most successful if administered in the preclinical or very early clinical stages of AD. A primary goal of this proposed consortium is to study the earliest manifestations of AD in order to develop effective tools to diagnose the disorder as early as possible which can lead to more effective treatments. In this application, we are committed to continuing the development of a consortium established in the previous grant cycle of dedicated AD research centers in Florida involving the University of Miami School of Medicine (UM), the University of Florida College of Medicine (UF), the Wien Center for Alzheimer's Disease at Mount Sinai Medical Center (MSMC) and the Center for Advanced Technology and Education at Florida International University (FIU). We aim to develop novel neuropsychological measures, functional assessments and novel imaging techniques for culturally diverse populations that are sensitive to the earliest manifestations of AD. With a sophisticated data repository that allows easy transfer of clinical across clinical sites, we aim to develop computerized diagnostic algorithms using multimodal data that will allow for the standardized and sensitive diagnosis of early AD. This work is critical in expanding infrastructure that will enable Florida to secure federal funds for important longitudinal studies and to serve as a national model for early detection and treatment of early Alzheimer's Disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Claes Wahlstedt	University of Miami	Epigenetic Modulation of Alzheimer's Disease Hallmarks	To date, all of the FDA-approved Alzheimer's disease (AD) treatments are palliative and do not target the main hallmark of the disease, beta-amyloid (Aβ) peptides that aggregate into amyloid plaques in the brain of patients and animal models. This is alarming since the Alzheimer's Association estimates that someone in the United States of America develops AD every 68 seconds and that the rate will increase to every 33 seconds by the year 2050. In Florida alone, the Department of Elder affairs estimates that about 450,000 people currently live with AD. Experts agree that new approaches to treating this disease are desperately needed to avoid a healthcare crisis in the near future. Our lab has successfully devised approaches to epigenetically target the hallmarks of AD. Using small molecules, we can successfully target the gene expression of culprits responsible for the production of Aβ as well as other AD-related proteins. This is exciting because the "amyloid cascade hypothesis" places Aβ at the origin of AD, causing a chain of molecular events leading to neuronal degeneration, memory loss, motor impairment, and eventually death. The Aβ peptide is the product of the amyloidogenic processing of the amyloid precursor protein (APP) through sequential cleavage by β-secretase and γ-secretase enzymes. Many attempts have been made to block the activity of these enzymes in AD. Drugs targeting γ-secretase have all failed due to undesirable side effects, and drugs targeting β-secretase activity have been difficult to design and implement. Surprisingly, few studies have targeted the non-amyloidogenic pathway where α-secretase cleaves APP within the Aβ sequence and precludes the formation of Aβ after γ-secretase cleavage. With our epigenetic approach, we can target both β-secretase and α-secretase at the gene level. Our preliminary data suggest that it is possible to significantly reduce Aβ and concomitantly upregulate the expression of such genes as the neuro-protective protein BDNF and α-secretase (ADAM10) with a small molecule purported histone deacetylase inhibitor (HDACi), CTI-309. We also show that treatment of normal mice with CTI-309 results in significant increase in Bdnf gene expression and decrease in tau gene expression in the brain. More recently, we show in a well-established AD mouse model that CTI-309 significantly increases learning and memory without any adverse effects. Although some HDACi have been proposed as cognitive enhancers, this is the first time an HDACi has been reported to affect the non-amyloidogenic pathway. Recently, we identified molecules that have good safety profiles, have already been in clinical trials for other diseases, and present beneficial effects against AD, similar to CTI-309. We propose to test these clinical candidates in AD mouse models and in patient-derived neurons. Such a safe drug could move to Alzheimer's clinical trials more swiftly and cost effectively than CTI- 309. We also recently identified a novel compound, CTI-350, that reduces β-secretase and Tau expression (main constituent of neurofibrillary tangles, the other hallmark of AD), targeting only one HDAC. We propose to test this compound in AD mouse models and to generate clinically relevant analogous compounds based on the results.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Antonio Terracciano	Florida State University	Optimization of "Powerful Tools" for Caregivers of Dementia Patients	As Alzheimer's disease and other dementias progress, behavioral expressions such as agitation, wandering, aggression, and changes in mood become more severe. These behavioral and psychological symptoms of dementia decrease quality of life, are linked to a faster progression of the disease, and increased costs of care. Caregivers often become overwhelmed and burdened by these behavioral manifestations, which precipitate the placement of adults with dementia in nursing homes. These behaviors are often managed with antipsychotics, but the off-label use of these medications is linked to severe adverse effects, including death. There is thus an urgent need to identify alternative treatments that are safe and effective. Family caregiver trainings and similar non-pharmacological interventions have shown some promise in addressing behavioral expressions. The objective of this proposal is to conduct a clinical trial to evaluate and enhance the clinical translation of a caregiver psychoeducational training. The intervention, Powerful Tools for Caregivers, is a 6-week, scripted educational program for family caregivers implemented in a group setting led by two trained group leaders. Powerful Tools for Caregivers is recognized as an evidence-based program by the Administration for Community Living, Administration on Aging. As part of a recently funded cooperative agreement with the Health Resources and Services Administration (HRSA), we will train new group leaders and implement the Powerful Tools for Caregivers program in communities across Florida. As part of this proposed study, we plan to leverage the HRSA-funded program to further evaluate and optimize the delivery of the Powerful Tool for Caregivers program. We will test whether the intervention reduces caregivers' stress and improves self-care, coping skills, and quality of life. In addition to caregiver outcomes, we will test whether the intervention reduces care recipients' behavioral expressions. The project will also examine the translational impact of training different types of group leaders and the cost-effectiveness of the intervention. This study is innovative in its focus on behavioral expressions and will complement and enhance the implementation of a psychoeducational program into diverse community settings. The study addresses several elements of priority area 1 of the Ed and Ethel Moore Alzheimer's Disease Research Program and the National Plan to Address Alzheimer's Disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Ann Horgas	University of Florida	An Analgesic Trial to Reduce Pain and Behavior Disruptions in Nursing Home Residents with Alzheimer's Disease	Behavioral expressions, which include agitation and aggression, affect up to 90% of persons with dementia and are a major source of patient and caregiver distress, nursing home placement, antipsychotic medication use, restraints, and increased health care costs. Our research suggests that one contributing factor to these behavioral expressions may be undiagnosed and untreated pain. Indeed, this was supported in a recent study of Florida nursing home residents. We found that residents with dementia and pain displayed more aggression and agitation than residents without pain. Pain assessment in persons with dementia is complicated because many patients experience impairments related to memory, judgment, and verbal communication. However, to date, no scientific evidence indicates that persons with dementia experience less pain; rather, they appear less able to recognize and verbally communicate the presence of pain. In a pilot study to treat pain in adults with dementia, we found that acetaminophen reduced behavioral expressions of pain, which returned to baseline after treatment stopped. Thus, our findings indicate that persons with Alzheimer's disease may have undiagnosed and untreated pain, which may lead to an increase in aggression and agitation. Primary Aim: To evaluate the effectiveness of routinely administered acetaminophen (1,000 mg, every 8h) in reducing behavioral expressions of dementia (e.g., agitation and aggression) in long-term care residents with moderate-to-severe Alzheimer's disease, due to reduced untreated pain. Research Approach. Thirty (30) older adults with moderate to severe Alzheimer's disease will be enrolled in the study. The sample will be enrolled from long-term care facilities in the North/Central Florida (Gainesville) region. A randomized, double-blind, placebo, cross-over design will be used. Participants will be randomly assigned to either treatment (1,000 mg orally, every 8 hours for four weeks; maximum dose = 3,000 mg per 24 hours) or control. The initial treatment phase will last for 4 weeks, and then the treatments will be reversed for the second 4 week period. The study medications will be prepared by an independent pharmacist to maintain blinding of all study personnel. The primary outcomes will be agitation and aggression and pain. Our goal to add more evidence for the effectiveness of treating pain as a mechanism for reducing agitation and aggression in PWD, using only mild analgesics.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
David Meckles	Florida State University	Blood Exosomes and Neurodegenerative Disease	Exosomes are small vesicles secreted from cells that circulate in the blood and other bodily fluids including urine, saliva, and cerebral spinal fluid. Exosomes carry proteins and other cellular factors that allow cells to communicate with each other. Evidence suggests that exosomes play a role in the progression of Alzheimer's disease (AD) by transporting unwanted material between cells. The molecular information contained within exosomes may be useful in early detection of AD. Exosomes are secreted from nearly every cell type investigated; therefore, exosomes in the blood represent a complex mixture from diverse sources. For exosomes to be used routinely for diagnostic purposes it will be imperative to harvest, and enrich for exosomes originating from the brain. This study will address the current limitations of exosome-based diagnostics and provide novel strategies for molecular-based epidemiological studies. Our objectives for the study are twofold: 1) to develop techniques for identifying tissue origins of circulating exosomes, and 2) to compare and characterize brain-derived exosomes present in human blood samples from healthy, mild cognitively impaired, and AD patients. We will apply information gained from these studies to FSU College of Medicine's geographically distributed campuses and associated large clinical network including rural and minority populations. We are well positioned to make significant advances on this area of research as our group has already developed new methods for the isolation and characterization of exosomes from blood. Overall, the proposed research will provide a novel way to detect AD risk by isolating brain-specific exosomes for early characterization. These findings will pave the way for understanding the epidemiological distribution of exosome markers in patients across the State of Florida.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
John Lucas	Mayo Clinic Jacksonville	Neuropsychological Norms for Ethnically Diverse Florida Elders	The National Institute on Aging and Alzheimer's Association (NIA/AA) workgroup on mild cognitive impairment (MCI) and Alzheimer's disease (AD) recommends that diagnoses of MCI and dementia be based on clear evidence of cognitive impairment beyond what would be expected for a given individual. Formal neuropsychological testing includes the standardized assessment of cognitive domains such as memory, naming ability, visuospatial ability, and executive functions, and offers a gold standard for objective, quantitative assessment of cognitive status and cognitive change over time. The diagnostic validity and clinical utility of neuropsychological measures, however, are highly dependent on the normative data used to interpret test performances. Most neuropsychological tests in clinical use today provide corrections for an individual's age and years of education attained, but few measures provide corrections for other demographic and sociocultural variables that have also been shown in the literature to have significant influences on test performances in older adults. Failure to account for these variables, such as ethnicity, literacy, primary language, and socioeconomic status, can lead to a disproportionate number of cognitively normal individuals from ethnically diverse backgrounds being misdiagnosed as having MCI or early dementia. Such misdiagnosis causes unnecessary anxiety among patients and their loved ones and can lead to the initiation of unnecessary treatment. In research settings, clinical trial outcomes may be compromised by the inclusion of individuals who do not have a progressive cognitive disorder and exclusion of individuals in the early stages of disease who are inaccurately diagnosed as having more severe dementia based on cognitive test scores. The proposed effort will establish a neuropsychological consortium and electronic database among three centers across the State of Florida: Mayo Clinic Florida (Jacksonville), University of South Florida (Tampa), and Mt. Sinai Medical Center (Miami). Consortium members will collect a common set of demographic, health, and sociocultural information and will administer a standardized battery of neuropsychological tests to a sample of 450 cognitively normal, ethnically diverse Florida elders (150 White, non-Hispanic; 150 Black/African American, non-Hispanic; 150 Hispanic). Investigators will derive regression-based normative corrections that can be applied to neuropsychological test performances. Because the normative sample will more closely match Florida's elderly population, the new Florida norms will improve diagnostics accuracy and clinical utility of neuropsychological testing when used to detect MCI and early dementia.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Jungsu Kim	Mayo Clinic Jacksonville	Targeting ApoE for Alzheimer's Disease Drug Discovery	Alzheimer's disease is the most common cause of dementia in the elderly. Accumulation of amyloid-beta peptide is hypothesized to initiate a pathogenic cascade leading to Alzheimer's disease. Apolipoprotein E (ApoE) 4 genotype is the strongest genetic risk factor for Alzheimer's disease. Therefore, understanding the molecular mechanisms underlying apoE metabolism will provide critical insights into apoE's role in Alzheimer's disease pathogenesis. ApoE protein binds to lipids and regulates the amount of lipids in the brain cells. We have previously demonstrated that overexpression of apoE receptor, low-density lipoprotein receptor (LDLR), in the brain strongly inhibits amyloid deposition and plaque-associated pathology. Furthermore, LDLR overexpression increased brain amyloid-beta clearance in a mouse model of beta-amyloidosis. Therefore, increasing LDLR protein levels in the brain may represent a novel Alzheimer's disease treatment strategy. Interestingly, increasing LDLR levels in the peripheral tissues, such as liver, is also being pursed to treat Atherosclerosis and coronary heart diseases. Therefore, targeting LDLR may represent a novel therapeutic approach for both Alzheimer's disease and cardiovascular disorder. Here, we propose to regulate LDLR level in a mouse model of beta- amyloidosis by modulating a novel LDLR-interacting protein. To test our hypothesis, we will determine whether a novel LDLR-interacting protein will affect amyloid deposition in the brain by using a gene therapy approach. In addition, we will screen small molecule libraries to identify lead compounds as potential drug candidates.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Rodney Guttman	University of West Florida	Enhancing Detection of Alzheimer's Disease Biomarkers Using Phage-derived Quantification (PdQ)	It is generally thought that the brain undergoes changes many years, perhaps decades before current clinical measures can detect the presence of dementia. However, a major obstacle to the prevention, treatment or cure for Alzheimer's disease is the inability to sensitively detect these changes. This proposal is designed to address a major barrier to the early diagnosis of Alzheimer's disease and related disorders (ADRD) through the development of a highly sensitive and low-cost approach to detecting disease-relevant tau metabolites. The goal is to develop a phage-based method and quantification platform (PdQ) to increase sensitivity of detection for low-abundance tau forms that may be present in blood or other easily accessible biofluids. This platform will have multiple positive effects that include: earlier and more accurate clinical diagnosis, increased ability to monitor disease progression, and decreased financial burden faced by government and private citizens. To accomplish this goal the project has two aims: Aim 1. Identify phage with high affinity and selectivity for total tau, AD-relevant phosphorylated threonine 231, and phosphorylated threonine 181 on human tau protein. This aim will show that PdQ methods can differentially detect closely-related modifications of a disease-relevant protein. Aim 2. Refine and compare two PdQ system approaches using quantitative polymerase chain reaction (qPCR) and bacterial amplification of phage target complexes for detection and quantification. This aim will demonstrate the high sensitivity of the assay. Alzheimer's disease is a slow, progressive neurodegenerative disease that ultimately results in death. It is the 6th leading cause of death in the U.S. and there is no cure. Current treatments are limited to a handful of medications that may improve some symptoms, but do not alter disease progression. For those with insurance, imaging technology can aid health care provider (HCP) in determining a diagnosis. However, only 45% of patients diagnosed with Alzheimer's disease or their caregivers report being told about the diagnosis by a HCP and therefore most wonder why they continue to experience cognitive, emotional, and physical declines. The current proposal addresses these concerns by developing a low-cost method to identify current or future biomarker proteins as our understanding of AD neuropathology improves. As a consequent, the successful completion of this proposal will allow earlier and more accurate diagnosis.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Dawn Bowers	University of Florida	Pilot Intervention in Mild Cognitive Impairment: A Proof of Concept Study with Transcranial Near Infrared Stimulation	This project proposes to pilot a non-invasive, low risk and low cost brain stimulation approach to enhancing cognition and mood in individuals with mild cognitive impairment who are at a high risk of transitioning to Alzheimer's disease. This stimulation technology uses red and near- infrared light (NIR) applied to the scalp, which passes through the skull and reaches brain tissue. Prior research in cellular and animal models demonstrates that red and NIR light is neuroprotective and increases the energy available to neurons. Several preliminary human studies have been conducted in young adults, stroke patients, traumatic brain injury patients, and individuals with major depression and anxiety. These studies have found improved thinking and memory, as well as improved mood. More studies are needed to examine this novel technology, particularly in determining if this approach can help pre-Alzheimer's disease individuals who are beginning to experience cognitive problems and psychological distress. Twenty individuals with mild cognitive impairment (MCI) will be recruited to participate in the study through a multidisciplinary dementia clinic at the University of Florida. This project will be conducted as a double blind randomized control trial, employing an active NIR stimulation group and a sham stimulation group. Participants in the trial will undergo 3 stimulation sessions per week, for two weeks using red and near infrared light produced from clusters of light emitting diodes placed over the head. Each session will last around 45 minutes. Active and sham groups will experience identical conditions except for stimulation by invisible infrared light. All participants will be asked to fill out mood questionnaires and will be tested on thinking and memory tests, some of which show a relationship with AD-related brain changes, such as temporal lobe atrophy. The technology investigated in this trial is relatively inexpensive, safe, painless, non-invasive and has no serious side effects. With few other treatment options available for individuals experiencing cognitive changes in older adulthood, there is an urgent need to develop additional intervention tools. The current study draws heavily on prior animal and human research to pilot an approach that has not been tested in those are at risk for AD. Transcranial NIR light is an understudied intervention that could represent a strategy for enhancing thinking and memory in persons with Alzheimer's Disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Glenn Smith	University of Florida	Consortium Study of Neuroimaging Impact of Behavioral Interventions in Mild Cognitive Impairment	There are currently no effective medications for those with Mild Cognitive Impairment (MCI) due to Alzheimer's or other diseases. Rather, behavioral interventions, especially cognitive remediation interventions, provide the most useful approach to addressing the behavioral and social needs of those with MCIs. The Principal Investigator (Dr. Smith) and Co-Principal Investigator (Dr. Chandler) for this proposal have a long-standing research collaboration examining which behavioral interventions may be most helpful in delaying progression to dementia for people with MCI. In this project, a three-site consortium will be established to extend this research and add to the number of Florida Memory Disorders Clinics that have the capacity to do this kind of behavioral research and offer this kind of clinical service. In addition to the central aim of expanding clinical research capacity in Florida this grant is configured to address a critical scientific question. It will compare two promising behavioral interventions (computerized brain fitness and yoga) to each other and to a control arm (wellness education). The impact on cognition, function and quality of life will also be studied. Moreover, neuroimaging will be used to estimate the post-intervention neuronal plasticity changes associated with this behavioral intervention in people with Mild Cognitive Impairment. The long-range goal is to build a network of Memory Disorders Centers with the capacity to test hypotheses that both behavioral interventions, including brain fitness and mind-body (yoga) cognitive remediation strategies will aid in slowing the progression of mild cognitive impairment through different mechanisms. Brain fitness programs will primarily improve cognitive function by increasing the functional integrity of the brain's cortical hubs (highly connected regions) due to more efficient information processing, while yoga primarily will increase global and regional cerebral perfusion. If these effects are present we will determine if either or both mechanisms also decrease pathology-related atrophy. This effort will enlarge this collaborative team, and generate a robust Florida network for behavioral intervention research and delivery of 'prevention' services. This proposal will also provide preliminary data for a subsequent longer, larger, Florida-led, multisite study to be submitted to the National Institute of Aging.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Shanna Burke	Florida International University	Demographic, Neuropsychological and Functional Classification, Risk Factors, and Progression Rates of Individuals in the National Alzheimer's Coordinating Center Database using Algorithmic Diagnosis.	"This study seeks to trial an enhancement of the diagnostic algorithm that intends to classify individuals based on results from neuropsychological testing and clinical dementia ratings. Specifically, this study plans to objectively test the central hypothesis by pursuing the following goals. First, older adults will be self-classified into well-defined cognitive status entities, such as cognitively normal, impaired but not Mild Cognitive Impairment (MCI), amnestic MCI, non-amnestic MCI, and dementia, using a diagnostic algorithm that considers a combination of amnestic and non-amnestic neuropsychological tests scores and its assigned clinical dementia rating. We will, then, explore the participants' demographic characteristics, protective factors, and risk factors associated with cognitive status subtypes. Once the cognitive subtypes are established, as well as, their associated characteristics, risk factors, and protective factors, the rates of progression from one cognitive subtype to another, over a period, will be examined. This expert system, algorithmic diagnostic software, will be freely distributed as open source software and available for download on the popular open source software sharing site, github.com. The proposed study is directly applicable to Priority Area 3, with a specific focus on area 3.5: expert diagnosis system. In under resourced and understaffed health care settings, the technology proposed herein has the potential to allow free-standing memory disorder clinics and primary care facilities to provide the expert detection and diagnostic services generally delivered by University Centers. Given that the Alzheimer's disease pathophysiological process likely begins 10 to 20 years prior to any observable symptoms, it is crucial to understand the early contributing risk factors, which may be revealed through an algorithm that can quickly, precisely, and simultaneously account for multiple variables. According to the Pew Research Institute (2015), 53 of 67 counties in Florida have an above-average share of people 65 and older when compared with the percentage (14.5%) of Americans (46.2 million) in that age range. This population is expected to grow over the next 20 years. The Department of Elder Affairs in the State of Florida reports "there are 500,000 individuals living with Alzheimer's disease [in Florida]. By 2020, it is anticipated that 580,000 individuals will be living with Alzheimer's disease. Nearly 12% of Florida senior population has been diagnosed with Alzheimer's disease." As the state's population grows, yet economic resources remain stagnant, it is imperative to focus on cost-saving strategies to provide memory care diagnosis and services to a growing elderly population. This project has the potential to affect not only a large share of the current aging population in Florida, but, also, the country, as Florida continues to attract older adults in the winter months and as a prime retirement destination."

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
David Kang	University of South Florida	Structure Activity Characterization of Novel Slingshot Inhibitors	Alzheimer's disease (AD) is a devastating neurodegenerative disorder of the brain that afflicts more than 5.4 million people in the United States and close to 500,000 people in Florida. At present, however, there are no effective treatment or therapy for AD. Two major pathologies – namely amyloid plaques and tau tangles – are responsible for the neurodegenerative changes seen in AD brains. While amyloid pathology is thought to initiate AD, tau is essential to execute the progressive neurodegeneration seen in AD. Previous studies in this lab have found that the Slingshot-Cofilin pathway not only promotes amyloid production but also links amyloid with tau pathologies. Recently, this lab has identified several promising Slingshot inhibitor compounds that not only reduce amyloid production but also inhibit the toxic amyloid signaling to tau. In this project, a combination of chemical, biochemical, cellular, structural, and computational techniques will be used to determine the structure activity-relationship between the compounds and Slingshot activity, focused on pathologically-relevant outcomes. This will allow for the optimization of these small molecule compounds to more effectively target the pathological process. As such, the results of this study are expected to lead to the identification of promising novel drug-like compounds that can potentially combat AD, as well as, determine the mechanisms of action of Slingshot and Cofilin in modifying AD pathology.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Richard Rotundo	University of Miami	Enhanced Acetylcholinesterase Expression Induced by Donepezil and Galantamine	Acetylcholinesterase (AChE) is the enzyme responsible for terminating neurotransmission at cholinergic synapses in the central and peripheral nervous systems in virtually every animal species. For this reason, tens of thousands of AChE inhibitors have been developed over the past 80 years for use as pesticides, nerve agents and therapeutic drugs for the treatment of disorders such as myasthenia gravis and Alzheimer's disease. The underlying assumption in all these applications is that AChE inhibitors act solely to reduce or eliminate its catalytic activity thereby increasing available acetylcholine at the synapse. In contrast, unpublished preliminary studies in our lab show that a subset of these inhibitors, such as those used for the treatment of dementias, also act as pharmacological chaperones to enhance the folding of newly-synthesized AChE. This in turn increases the production of catalytically active enzyme molecules. The net result is an increase in the synaptic form of AChE in the CNS with the potential to reverse the desired effects of these drugs. In addition, these results suggest a plausible explanation for the "sundown" effect observed in many Alzheimer's patients where their symptoms appear worse at the end of the day after taking these drugs. The specific aims of this proposal are: 1) to determine in detail using tissue cultured cells which types of AChE inhibitors enhance enzyme folding as opposed to only inhibiting enzyme activity, the desired effect for the treatment of Alzheimer's disease; 2) to determine whether they exert the same effects on AChE folding in vivo compared to carbamate type inhibitors such as rivastigmine or neostigmine using a mouse model; 3) to test the hypothesis that a combination of an active site directed inhibitor such as donepezil or galantamine together with a carbamate type AChE inhibitor such as rivastigmine or neostigmine, anticholinesterases already in clinical use that are predicted to not enhance AChE folding, may give superior memory retention using a mouse model. These studies will clarify the molecular mechanisms of this novel and unpredicted side effect of the two major drugs used for treating Alzheimer's disease. More importantly, they will provide a possible solution to the problem by reducing the effects of these drugs on AChE folding while maintaining elevated acetylcholine levels through sustained inhibition using alternative AChE inhibitors.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Pamela McLean	Mayo Clinic Jacksonville	How does alpha-synuclein contribute to tau dysfunction in AD?	The main pathological features of Alzheimer's disease (AD) are the formation of plaques and neurofibrillary tangles in the brain, composed of beta-amyloid (Abeta) and MAPT (tau) proteins, respectively. In another form of dementia called dementia with Lewy bodies (DLB), as well as, Parkinson's disease (PD), alpha-synuclein (asyn) is the major pathological protein. Although the aggregation of Abeta, tau, and asyn are used as the major pathological markers of AD and PD, respectively, there is ample evidence that these pathogenic proteins are closely linked in neurodegenerative diseases. Importantly, AD patients with asyn pathology usually present with a more rapid cognitive decline and shortened survival time compared to AD patients without asyn pathology. In human Alzheimer's disease brains, tau and asyn pathology are often found together in the same neuron. There is also increasing evidence that tau is a presynaptic protein, much like asyn, and that tau and asyn may interact at cellular membranes. In this application, this lab will try to determine if there are previously undetected forms of asyn and tau in Alzheimer disease postmortem brains that could contribute to disease, and we will use neurodegenerative model systems to probe a role for tau-asyn interactions in the progression of Alzheimer's disease and other dementias. Human post-mortem brain samples, from the Mayo Clinic Brain Bank, will be used to determine if a tau-asyn interaction is prevalent in AD14 compared to other neurodegenerative diseases and healthy controls. In addition, a novel mouse model with abundant tau pathology and the associated behavioral phenotype will be used to determine if co-expression of asyn exacerbates the phenotype, shortens survival time, and increases pathology. This project addresses the objectives of the Ed and Ethel Moore Alzheimer's Research Program by proposing to validate asyn as a novel therapeutic target for AD and by providing insight into possible pathological mechanisms. Investigating asyn as a target for therapeutics is appropriate, given the considerable evidence that AD is a complex proteinopathy, which commonly has comorbid asyn pathology, and displays overlapping symptoms with other neurodegenerative diseases

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Jennifer Bizon	University of Florida	Impact of perirhinal cortical tau pathology on pre-clinical cognitive decline	Accumulation of tau proteins is a pathological hallmark of Alzheimer's disease that initially emerges in a brain region referred to as the transentorhinal subregion of the perirhinal cortex. Viral-based technology, which allows human pathological genes to be expressed in animal models, has been useful for conducting preclinical investigation to better understand how tau proteins contribute to the development and progression of Alzheimer's disease. These preclinical models, however, have, thus far, exclusively employed young subjects and have not yet incorporated the neuroanatomical features of human disease pathology. Even in the absence of pathology, the aged brain has several biological features that differ from young subjects and that could influence disease processes. As Alzheimer's disease develops against the backdrop of an aging brain, it is critical to elucidate how aging and pathological tau interact to influence disease mechanisms and cognitive outcomes associated with Alzheimer's disease. The first goal of this research is to establish a rat model of pre-clinical Alzheimer's disease in which viral-mediated gene transfer will be used to drive the expression of human toxic tau species in the perirhinal cortex of an aged rat. The perirhinal cortex receives input from all sensory modalities, and is critical for the perception of highly processed sensory representations integral for memory formation. This lab has developed and validated highly sensitive behavioral assays of perirhinal cortical function that strongly predict memory in preclinical animal models. The secondary goal of this proposal is to establish these behavioral assays as a biomarker for early detection and tracking of disease pathology in patient populations.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Minerva Carrasquillo	Mayo Clinic Jacksonville	Early detection biomarkers of Alzheimer's disease inflammation and vascular risk factors in African Americans	Alzheimer's disease (AD) is a growing epidemic that is having an increased impact on society as life expectancies rise. Up to 74% of the risk for AD can be attributed to genetic factors; therefore, improving our knowledge of the underlying genetic risk factors is essential to our understanding of the disease pathomechanism, and for the development of treatments and prevention. Although AD is twice as prevalent in African-Americans as in subjects of European descent, the vast majority of genetic studies aimed to identify AD risk factors have been limited to Caucasian populations. Given that there is also a higher risk of cardiovascular disease in African-Americans, and the strong evidence for a link between vascular disease and AD, the long-term goal of this proposal is to improve the understanding of the influence of vascular disease risk factors and inflammation on AD in this minority population. Specifically, this proposal aims to identify genetic variants that influence genes involved in inflammation or vascular function, in African-Americans, and to develop minimally invasive blood and plasma biomarkers to aid in early disease diagnosis. The knowledge gained from this study could also lead to new and more relevant treatments, and ultimately preventive therapies. This funding opportunity will enable targeted analysis of genes/proteins involved in inflammation and vascular health through (1) a thorough screen for genetic variants that associate with AD in the Mayo Clinic African-American AD case-control series in targeted genes, (2) identification of altered blood gene expression or plasma protein levels, in AD vs. non-ADs for targeted genes/proteins (3) development of early detection biomarkers through the correlation of AD age-at-onset with (a) blood gene expression and (b) plasma protein levels of targeted genes. The current application would address all three focus areas in Priority Area 4 of the 2016 Funding Opportunity Announcement released by the Florida Health, Ed and Ethel Moore Alzheimer's Disease Research Program, as the proposed studies focus on AD in African-Americans, an understudied population in which AD is twice as prevalent as in Caucasians (Focus Area 4.1.), aim to identify vascular risk factors that contribute to AD (Focus Area 4.2), and aim to develop minimally invasive early detection biomarkers (Focus Area 4.3).

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Dennis Dickson	Mayo Clinic Jacksonville	Pathophysiology of Traumatic Brain Injury in the State of Florida Alzheimer's Disease Initiative Brain Bank	Traumatic brain injury (TBI) is a strong environmental risk factor for the development of dementia, including Alzheimer's disease (AD). The associative risk between TBI and dementia has been reported to be 'dose-dependent', or based on the severity of TBI and number of TBI. In this regard, repetitive TBI can result in a neurodegenerative disorder known as chronic traumatic encephalopathy (CTE). The most well-defined sources of repetitive TBI that can lead to CTE are sustained through contact sports participation (football, boxing, soccer, wrestling, and others) or military blast exposure (improvised explosive devices). CTE is a neuropathologically-defined disorder with characteristic abnormal deposits of the protein tau in neurons and astrocytes at the depths of folds in the brain ('cerebral sulci') and surrounding blood vessels. While CTE pathology may exist as the sole brain pathology in certain cases, many cases (especially older individuals) harbor comorbid brain pathologies consisting of CTE, as well as, other neurodegenerative pathologies. Senile plaques, the hallmark lesions of AD, are observed in over half of CTE cases, and have been reported to increase with CTE severity. Due to the complex relationship between TBI, CTE, and AD, there exists a need to clarify 1) how TBI can lead to these combined pathologies, 2) whether the presence of CTE pathology modifies AD pathology and vice versa, 3) how the combination of CTE and AD affects the clinical picture of dementia, and 4) whether there are specific risk factors which predispose individuals to both CTE and AD. In this proposed study, we will search for CTE and other TBI pathologies in the Alzheimer's Disease Initiative (ADI) Brain Bank, a brain banking program sponsored by the state of Florida's Department of Elder Affairs. Within the ADI Brain Bank, 1,004 brains meet neuropathology diagnostic criteria for AD. It is proposed to screen these brains for CTE tau pathology and comparing these findings to information extracted from clinical records pertaining to demographics (gender, race, education, alcohol/tobacco use), neurodegenerative disease (family history, disease onset, disease duration, age at death), traumatic brain injury (sporting-related trauma, non-sporting related trauma), psychiatric impairment (depression, anxiety, obsessive compulsive disorder, posttraumatic stress disorder), and clinical cognitive assessment scores. Finally, using DNA (deoxyribonucleic acid) from these 889/1,004 cases, we will attempt to identify genetic risk factors in cases with CTE and TBI pathology not found in cases without CTE and TBI pathology. These findings will give important insight toward understanding the pathophysiology of TBI and its contribution to AD progression.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Philip Harvey	University of Miami	Post-doctoral Research Fellowship	There is a pressing need to train promising researchers to study more innovative ways of assessing and diagnosing persons in the earliest stages of Alzheimer's disease (AD). Early diagnosis paves the way for increasingly more targeted treatment interventions. This application presents an unprecedented opportunity for post-doctoral neuropsychology fellowship training to a) study the earliest Preclinical manifestations of AD; b) participate in the development and implementation of novel measures to assess Pre-clinical AD; c) learn to clinically evaluate different ethnic and cultural groups for early stage mild-cognitive impairment; d) learn how to interpret and to conduct research relating cognitive and functional test findings to biological measures of the brain and e) learn to publish papers and prepare NIH funded applications for further extramural grant support. The primary mentor for the fellow would be Philip Harvey, PhD, a prominent neuropsychologist and scientist who has a specialty in cognition, aging, and the development of novel functional assessment tools. Dr. David Loewenstein, PhD, ABPP, a board-certified neuropsychologist, Director of the Division of Neuropsychology and Professor of Psychiatry and Behavioral Sciences at the Miller School of Medicine at the University of Miami Miller School of Medicine would be the fellow's Primary Co-Mentor. Together, Drs. Loewenstein and Harvey have pioneered novel functional assessment in neurologically vulnerable individuals including those at risk for AD. Dr. Loewenstein is currently the Principal Investigator (PI) of a five year National Institutes of Health (NIH) R01 grant studying novel cognitive paradigms for the prediction of cognitive decline in the elderly. He is also co-leader of the Clinical Core and Scientific Project Director of the newly funded Alzheimer's Disease Research Center (ADRC) located at Mount Sinai Medical Center that relates novel cognitive and brain biomarkers to cognitive decline in Preclinical AD in Hispanic and Non-Hispanic populations. Dr. Harvey would also be assisted by co-mentor Dr. Rosie E. Curiel, (University of Miami); an Assistant Professor and co-investigator on the abovementioned projects who actively mentors an Ed and Ethel Moore postdoctoral fellow. Dr. Curiel is a geriatric neuropsychologist who focuses on cross-cultural neuropsychological assessment. These mentors can provide an unprecedented opportunity for a postdoctoral fellow to gain extensive research and clinical diagnostic experience. The proposed fellowship will help cultivate fresh talent into the critical area of early diagnosis of older adults representing different cross-cultural groups, provide excellent academic mentorship by distinguished investigators and clinicians and prepare the individual for asuccessful career in clinical patient oriented research.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Christopher Janus	University of Florida	Corticotropin-releasing hormone (CRH) Immunotherapy for Alzheimer's disease	Alzheimer's disease (AD) is the most widespread cause of dementia among elderly populations, affecting more than 37 million people worldwide according to the 2009 census. Recent clinical reports indicate that chronic stress may significantly increase the risk of developing AD. Also, other stress related diseases, like posttraumatic stress disorder or depression, significantly increase risks for the development of dementia. The physiological response to stress is the activation of hormonal response in the brain and adrenal glands (so called hypothalamic-pituitaryadrenal axis (HPA)), with the purpose to restore the hormonal balance of the body. The small peptide, called corticotropin-releasing hormone (CRH) constitutes the primary response to stress. If stress persists, then the excessively higher levels of CRH lead to long-term dysregulation of HPA, which causes increases in levels of amyloid beta (Aβ) and tau abnormal phosphorylation, as well as abnormal behavior of AD patients. The consequent chronic increased levels of plasma cortisol correlate with neuronal death in the brain and cognitive deficits, leading to AD dementia. It is proposed to selectively lower the levels of CRH in the brain with the purpose to stave off the cascade of deleterious pathological events leading to AD dementia. To this end, using mouse models of behavioral stress, it is proposed to test novel immunotherapeutic approaches to decrease CRH signaling in the brain. Initial data showing this lab's ability to induce a robust antiCRH response with a synthetic vaccine has already been collected. In this pilot study, the aim is to identify an optimized vaccination approach and to generate proof of concept data that will substantiate the hypothesis that lowering CRH levels prevents cognitive decline in a stressed mouse. These results will provide compelling evidence that CRH might be a viable potential target for intervention in AD.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Kiminobu Sugaya	University of Central Florida	Antibody targeting of IL1RAP and studying their therapeutic effects in mouse models of Alzheimer's disease	Alzheimer's disease (AD) is a devastating disease caused by a breakdown of brain networks involved in memory function. The disease pathology is multi-dimensional and several pathways are involved in disease progression. In AD, amyloid-β peptide (Aβ) is one the main proteins involved in pathology of AD. There is currently no therapy proven to stop or reverse the underlying cause of the progressive symptoms of Alzheimer's disease. Research needs to be focused on newer gene mechanisms that are responsible for the clearance of amyloid plaques, particularly in early stages of the disease (when symptoms are mild or not yet present). Recently, researchers have reported a variant in a gene (IL1RAP) associated with greater amyloid plaque accumulation. Based on several studies, it is suggested that targeting the protein (IL1RAP) will be a viable approach for faster clearance of amyloid deposits and for improvement in controlling Alzheimer's disease. It is proposed to use exosomes as delivery vehicles to deliver antibody that can stop the activity of IL1RAP, in order to decrease amyloid-β peptide formation in the Alzheimer mouse model. Brain cell (oligodendroglial) exosomes will be used as delivery vehicles. Recent studies have shown these exosomes are involved in improving the brain integrity. The important aspect is to increase the specificity target delivery of these exosomes. The surface of exosomes will be engineered to display brain homing peptides (BHP1). The BHP1 peptide will specifically direct the exosomes to the brain cells. The therapeutic antibody against IL1RAP will be attached to the exosomes using click chemistry. Alzheimer's disease patient derived induced pluripotent stem cells (iPS cells) will be used to study the effect of these new therapeutic delivery systems. Alzheimer's disease mouse models will also be used to study this novel therapeutic approach utilizing exosomes delivering antibodies to arrest the IL1RAP activity. The functional outcomes by the antibody treatment will be determined using magnetic resonance imaging (MRI), and behavioral and histological analysis. A transgenic mouse model or appropriate mouse model will be utilized to represent the Alzheimer disease pathology to study the effects of exosomal delivery of antibodies against IL1RAP. Exosomes have huge potential in utilization as a delivery vehicle; however, few studies have been done to utilize exosomes as antibody delivery vehicles in Alzheimer's disease. Exosomes have a natural ability to internalize into the cells and can exploit this nature of exosomes to deliver therapeutic proteins to neuronal cells.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Diego Rincon-Limas	University of Florida	Large-scale identification of genes that suppress concurrent Abeta42 and tau pathology in vivo	Alzheimer's disease (AD) is an incurable neurodegenerative disorder that causes progressive memory loss and cognitive impairment, leaving patients totally incapacitated. The two landmark lesions in Alzheimer's disease (AD) are extracellular amyloid plaques mainly formed by the amyloid beta-42 (Abeta42) peptide and intracellular neurofibrillary tangles containing aggregates of abnormal tau protein. Abeta42 and tau were thought of as independent culprits for a long time, but in light of recent studies, it is clear that they are intimately related and have synergistic activities. However, very little is known about how (and which) Abeta and tau interactions trigger AD pathogenesis, which significantly impedes the development of effective therapies. To address this, a new fly model of AD that genetically produces both human Abeta42 and tau has been created. These "humanized" flies display extracellular deposition of Abeta42, intracellular aggregation of pathological tau, and robust neurodegeneration. The robust pathology of these flies provides an ideal platform to conduct a large-scale identification of genes that can suppress Abeta42+tau neurotoxicity. Therefore, Abeta42+tau flies will be crossed with ~6,500 strains engineered to specifically silence individual fly genes that are also present in humans. First, a primary screen in the fly eye will be performed, which provides a fast-visual result of the effect of silencing every gene. Then, validation of the identified suppressors for behavioral functions, preservation of brain neurons, and development of pathological markers will be performed. It is anticipated that this experimental approach will uncover critical/novel targets for intervention not available to classical experimental models. Thus, the first large-scale attempt at discovering Abeta42+tau suppressors will not only provide information about disease mechanisms but also identify relevant therapeutic targets to approach this overwhelming disorder. This fits perfectly with the mission of the Ed and Ethel Moore Alzheimer's disease Research Program to "stimulate the discovery and validation of a broad spectrum of potential therapeutic targets for AD".

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Danielle Gulick	University of South Florida	CK1 delta inhibition to reduce sundowning in Alzheimer's disease	Alzheimer's disease is a progressive, devastating form of dementia that affects not only patients but, also, their caregivers, diminishing quality of life for everyone touched by the disease. Although a number of therapeutics are under study, no definitive treatment has been identified. Furthermore, many patients with Alzheimer's disease also struggle with sundowning syndrome, an increase in confusion, agitation, wandering, and aggression during the late afternoon and evening hours. This syndrome results from a loss of the internal clock that normally sets our daily circadian rhythms, and it is proposed that it can be treated with drugs that will reset the internal clock. To this end, two mouse models of sundowning syndrome will be used to test whether treatment with a drug that resets the circadian clock is sufficient to reduce the symptoms of sundowning. Thus, it is proposed that treating these models, as well as healthy controls, with an inhibitor of casein kinase 1, a key enzyme in the clock. This lab has shown that this inhibitor stabilizes the clock and improves cognition. During drug treatment, it will be assessed whether circadian rhythms are corrected by analyzing home-cage activity in the mice. In separate groups of mice, analysis of whether the drug is able to improve cognition, reduce anxiety, and improve socialization will be performed. These behaviors at four points in the day, every six hours, will be examined to determine whether the changes in behavior are due to a global improvement in function, or to a shift in the time when symptoms are at their worst. In addition, because casein kinase plays a role in the formation of the toxic beta-amyloid peptide that leads to neurodegeneration in Alzheimer's disease, levels of this peptide in mice treated with the inhibitor compared to control mice will be examined. This work will provide a foundation for drug development to improve the lives of patients with Alzheimer's disease and their caregivers by reducing some of the most severe symptoms of the disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Rosie Curiel	University of Miami	A Consortium to Study Precision-based Computerized Assessment for the Detection of Mild Cognitive Impairment in Older Adults	With the rapidly aging population, early detection of cognitive decline in individuals at risk for Alzheimer's disease (AD) is a global priority. It is now well-established knowledge that pathological changes occur in the brain decades before the onset of any detectable clinical symptoms. This understanding has shifted the priority in the field from clinical diagnosis and treatment, toward the aim of developing early targeted interventions and pre-symptomatic neuroprotective therapies. For these strategies to be optimally effective and successful, it is critical to accurately identify and target individuals at risk. This has led to a growing emphasis on discovering biological markers that may signal the emergence of preclinical AD states, such as Mild Cognitive Impairment (MCI), and highlighted the importance of capturing very subtle cognitive changes that transpire early in the disease course. Detecting cognitive changes are critical because cognitive changes are used to detect and track disease progression over time from MCI to early AD. In addition, a meaningful change in cognitive status represents a measurable clinical outcome. Traditional and widely used assessment paradigms such as delayed recall and rate of forgetting are not well suited to identify the subtle changes in cognition that manifest during the preclinical stages of AD and early MCI. In addition, they lack cross-cultural applicability, are lengthy, labor-intensive, vulnerable to human error, and associated with practice effects. To this end, the use of computerized testing batteries among older adults have been explored as a more suitable option to mitigate some of the above-mentioned limitations by increasing accessibility to distant sites, promoting efficiency, providing real-time data entry, and increasing the accuracy of recording responses and response time. However, a major problem with existing traditional computerized batteries is that they are automated versions of traditional neuropsychological tests that lack sensitivity to detect AD-related cognitive decline, and employ the same paradigms originally developed for the assessment of dementia or traumatic brain injury. Measures for early detection of cognitive impairment of Hispanic and non-Hispanic elderly persons that are, both, sensitive and portable, are in increasing demand as it is recognized that early diagnosis is the key to more effective intervention strategies. It is believed that the proposed work is positioned to be at the forefront of this critical area. Three novel computerized tests will be administered to 120 older adults (40 normal elderly, 40 amnestic mild cognitive impairment: [aMCI] and 40 Preclinical AD participants). Half of these subjects will be primary Spanish- speakers while the other half will be primary English speakers. Test – retest reliabilities for the experimental measures will be obtained and the discriminative validity of the instrument will also be examined and compared to traditional memory measures. This project is expected to provide critical data that parallels a recently submitted strong early career R01 grant application to the National Institutes of Health, which will examine changes in cognitive performance using these instruments as they relate to longitudinal biological changes within the brain.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Mariet Allen	Mayo Clinic Jacksonville	Identification of functional regulatory variants at Alzheimer's disease loci	Alzheimer's disease (AD), is the most common form of dementia affecting the elderly, and is known to have a substantial genetic component. Identifying genetic variants that influence disease risk has led to improved understanding of the pathological processes involved in this disease and can greatly inform future research and therapeutic approaches. Furthermore, genetic risk factors and their expressed transcripts and proteins represent potential biomarkers for predicting disease risk and identifying subsets of individuals for targeted clinical treatment or prevention trials. Genomewide associations studies (GWAS), have identified more than 20 common genetic variants that influence risk for AD. This lab, and others, have shown that some of these variants also associate with expression levels of near-by genes. Importantly these findings implicate the biological mechanism of action (regulation of gene expression) and the likely influenced gene(s). However, GWAS are limited, in that the variants genotyped are largely thought to represent a locus (genomic region), rather than actual functional variants. Additional studies are needed, to fine-map the implicated loci and identify and validate the functional genetic risk variants. This proposal aims to address this knowledge gap by identifying, and annotating, regulatory variants at AD risk loci nominated by disease GWAS. Identifying these variants will reveal the biological basis for the disease risk association at these loci, provide novel insights into the pathophysiology of AD, and generate new leads for therapeutic strategies aimed at treating or curing this disease. Specifically, targeted next-generation sequencing will be used to identify variants that fall within the genetic locus tagged by the common variant(s) and any distal regulatory regions nominated by bioinformatics tools. Importantly, sequencing of subjects that were part of our published work that implicated transcriptional regulation as the likely mechanism at these loci and in which gene expression measures already exist. All identified variants will be evaluated for association with expression of genes within the locus using these existing expression measures. Additional resources such as variant annotation tools (Computer Assisted Drug Design, Regulome Database, and HaploReg Database) and available regulatory element annotation, will be used to further refine our selection of putative functional variants. Results from available data generated by the Alzheimer's disease sequencing project (ADSP) and the International Genomics of Alzheimer's Project (IGAP) will be used to evaluate the association of the nominated variants with AD risk, where possible. Nominated variants will be assessed in additional samples to confirm the association with gene expression measures, and finally tested in a cell based model, using reporter assays, to confirm the functional impact on gene expression. The expected outcome of the proposed work is the identification of functional regulatory variants at some of the known AD risk loci, which may provide novel insights into the pathophysiology of this disease and nominate therapeutic targets. The identified variants and influenced genes may also represent novel biomarkers for disease risk prediction, critical for design of successful therapeutic trials.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Pete Heinzelman	Mayo Clinic Jacksonville	Yeast Surface Display Engineering of Human Fibronectin Domains for Enhanced Brain Delivery of Alzheimer's Disease Therapeutics	More than ninety-five percent of potential Alzheimer's disease (AD) therapeutics and prophylactics have little or no ability to migrate from circulation to brain tissue. These blood-to brain transport limitations necessitate unfeasibly high doses of systemically administered drug to realize beneficial effects within the brain and/or promote off-target side effects throughout the body and thus prevent such transport-impaired molecules from being viable AD drug candidates. Developing a generalizable delivery technology that, both, targets transport-impaired drugs to the blood brain barrier (BBB), a tightly packed layer of endothelial cells surrounding the nutrient supplying blood vessels that radiate throughout the brain, and that facilitates transport of these drugs across the BBB, dramatically expanding this inventory of effective AD pharmaceuticals. This will transform the way clinicians seek to treat and prevent AD by providing the breadth of options needed to enable development of personalized AD treatment and prevention programs through evaluation of patient responses to different drug combinations. Conjugation of small molecule drug- loaded liposomes or protein drugs to 'Trojan Horse' antibodies that, both, bind to proteins and are transported across the BBB, is currently the most utilized strategy for targeting AD drugs to the central nervous system (CNS). Such Trojan Horse antibodies, however, bind to proteins expressed on the BBB, in addition to, many other endothelial tissues throughout the body. This ubiquitous expression results in less than one percent of systemically injected Trojan Horse antibody-drug conjugate doses reaching the brain. This research will address the above implied need for step change improvements in AD drug delivery by simultaneously identifying proteins and/or protein structural features that are specific to or highly enriched on BBB endothelial cells and generating human fibronectin domains (Fn3s), antibody-like biomolecule-binding proteins that are less expensive than antibodies to produce, that bind to these BBB- specific molecular entities and can be superior substitutes for existing Trojan Horse antibodies in targeting AD drugs to the CNS. Adaptation of microscale filtration techniques employed in household cleaner manufacturing to convert BBB endothelial cells into water soluble nanometer-23 sized vesicles, known as CytoBits, is the key innovation allowing engineering of highly specific BBB-binding Fn3s. Unlike whole cells, CytoBits are compatible with highthroughput screening methods that utilize magnetic-microspheres and flow cytometry, a microfluidics and fluorescence measurement assisted technique for high fidelity isolation of single yeast cells from populations numbering in the millions, that underlie yeast's surface. This technique display's its power as a technology platform for engineering proteins with binding properties that are well-suited to specific biomedical applications. In this work, yeast display will be utilized to isolate a collection of between twenty-five and fifty BBB-specific Fn3s from a library containing 250 million members; this substantial library size brings strength of numbers to addressing the BBB-binding specificity challenge by each member's Fn3 possessing unique biomolecular-binding properties. This brain-targeted, drug-carrying Fn3s will offer exciting potential to make AD treatment and prevention program personalization a reality.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Nilufer Ertekin-Taner	Mayo Clinic Jacksonville	Florida Consortium for African-American Alzheimer's Disease Studies (FCA3DS)	This proposal entitled "Florida Consortium for African-American Alzheimer's Disease Studies (FCA3DS)" stems from this team's highly successful prior study funded by the same mechanism. The current proposal will leverage the infrastructure and collaborations previously established during the initial grant (5AZ03, 01/12/2015-6/30/2015). The main motivation of this proposal is to enhance Alzheimer's disease (AD) research in African-Americans, which remain an understudied population despite being afflicted by this condition twice as frequently as whites. This team's ongoing and proposed research aims to overcome this knowledge gap, because studying diverse populations with distinct risk profiles is critical to the discovery of a wider array of both genetic and non-genetic risk factors for AD. Such discoveries are essential for the identification of drug targets, preventative measures and healthcare policies aimed at curing or delaying progression of AD, which is especially germane to high risk populations, like African-Americans. During the 5-month course of the prior grant, significant progress was made pertaining to a) sample collections (establishment of IRB approvals, streamlined sample and data collection protocols, training of personnel for sample handling at all sites); b) data generation (generation and quality control of whole exome sequence=WES data on 137 AD and 113 control subjects); and c) data management (generation of the relational FCA3DS database and importing of data into this database). During the following 6-month no- cost extension (7/1/2015-12/31/2015), all the known early-onset AD (EOAD) and late onset AD (LOAD) genes were screened and identified novel genetic variants in African-Americans different than those reported for whites. Specifically, risk variants were discovered in the ABCA7 gene that occurs at a higher frequency in African-American AD subjects. Further, additional variants were detected in two other genes (ZCWPW1, NME8) that showed association with memory scores in this population. Finally, two variants were identified in the EOAD genes PSEN1 and PSEN2. These findings are currently under review (LOAD) and in preparation (EOAD) for submission. Hence, the data that was generated under the prior Florida Health grant highlights the critical importance of studying diverse populations, underscores the potential of our approach and this team's ability to execute these studies. In the new proposal, the aims are to: 1) Expand the cohort for WES of additional samples; 2) Launch studies of gene expression pathways utilizing blood RNA samples; 3) Utilize plasma amyloid ß and cognition as biomarkers for novel gene/pathway identification. This consortium grant includes three Florida institutions: Mayo Clinic, University of Florida and Mount Sinai Medical Center. Expected outcomes are: 1) Establishment of a sizable African-American cohort with DNA sequence, gene expression, plasma amyloid ß data; 2) Targeted gene expression studies correlated with genetic and clinical outcomes. 3) Identification of novel genes/pathways implicated in AD risk, amyloid metabolism and cognition. This proposal is innovative in that AD gene/pathway discovery studies that utilize combined genetic /expression /protein /cognition data are unprecedented in African- Americans. Expected outcomes of this proposal include a unique resource and impactful pathophysiologic findings in this understudied population.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
David Loewenstein	University of Miami	Brain Amyloid Load And Novel Cognitive Measures in Diverse Ethinic Groups	This is an exciting study that examines amyloid load in the brain as it relates to the performance of novel cognitive stress tests designed to assess vulnerability to proactive semantic interference (PSI) or failure to recover from PSI to brain amyloid load, in two different ethnic and cultural groups of elderly participants (African-American and Hispanic). This data is essential in establishing the utility of novel cognitive stress tests in epidemiological and clinical studies. The proposed investigation is, both, an innovative, as well as, a critical study regarding the relationship between total and regional brain amyloid load and performance on both novel cognitive stress test measures among at risk African-American and Hispanic and White noncommunity-dwelling elders. The validation of cognitive stress tests against biological measures in different ethnic and cultural groups are critical for future epidemiological and clinical research in Alzheimer's disease and related disorders. This proposed work is a natural offshoot of a previously funded Ed and Ethel Moore State of Florida Grant (Loewenstein, PI) and an ongoing NIH longitudinal study (Loewenstein, Principal Investigator). In an important recent paper by Loewenstein et al., (2016) supported by the Ed and Ethel Moore Foundation, it was demonstrated that vulnerability to recovery from proactive interference, based on a novel cognitive stress test, could successfully distinguish between individuals with mild cognitive impairment (MCI), PreMCI (evidence of a history of cognitive decline but normal neuropsychological test results), subjective memory disorder and cognitively normal elders. A critical finding was that among a group of community dwelling elders with PreMCI, subjective memory disorder and no memory complaints (all of these groups that normal scores on traditional 5 of 6 neuropsychological tests), the failure to recover from proactive semantic interference was highly associated with brain amyloid load (an indication of accumulating fibrillar brain amyloid and a high risk factor for Alzheimer's Disease (AD) with $r=-.62$ ($p<.01$) for the precuneus and for the whole brain and ($r=-.60$ ($p<.01$). This exciting finding among predominantly white non-Hispanic elderly indicated that early deposits of brain amyloid in community-dwelling elders were highly related to an early cognitive-behavioral marker (inability to recover from proactive semantic interference). In the current proposal, existing resources will be leveraged from our ongoing R01 National Institutes of Health (NIH) study (that does not currently include measures of amyloid load) to provide 60 subjects who are well characterized as having mild cognitive impairment (MCI) or PreMCI (subjective memory impairment and clinical evidence of mild decline but neuropsychologically normal). All subjects will have Magnetic Resonance Imaging (MRI) scans of the brain. To study 30 African- American (AA) and 30 Hispanic older adults 60+ years who meet these criteria from a cohort of over 250 potential participants in the NIH study was proposed.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Yona Levites	University of Florida	Functionalized Intrabodies As Potential anti-Tau Therapy	To rapidly and cost-effectively evaluate potential modifiers of Alzheimer's disease (AD) pathology in mouse models, a "somatic brain transgenics" paradigm was developed, through the delivery of gene constructs packaged into adeno-associated viral vectors and, then, injected into the cerebral ventricles of P0 mice. The mechanisms underlying the abnormal phosphorylation and accumulation of Tau in AD remain unclear, but one of the possibilities is that it might be due to conformational changes in tau in the diseased brain. Anti-tau immunotherapy has recently emerged as a promising approach to target tau, but many mechanistic questions regarding the optimal form of anti-tau immunotherapy remain open. This lab has demonstrated that intracellularly expressed anti-tau intrabodies prevent Tau toxicity and formation of neurofibrillary tangles, and prolonged life span of transgenic mice. It is hypothesized that anti-Tau immunotherapy can be optimized by targeting Tau to proteasomal degradation, cellular machinery that is geared to process and eliminate unneeded or damaged proteins by proteolysis. Preliminary data suggests that Tau aggregation functional intrabodies in cell culture models successfully prevented accumulation of aggregated phospho-tau. It is proposed to further develop functionalized anti-Tau intrabodies and evaluate them in vivo in Tau transgenic mouse models. Possible mechanism of action of these functionalized intrabodies will also be examined. These studies will provide critical insights into i) whether targeting tau to proteasomal degradation is more efficacious and ii) whether this approach can be utilized toward other neurodegenerative diseases involving misfolded proteins.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Holly Cukier	University of Miami	The Role of TTC3 in Alzheimer's Disease Pathogenesis	Alzheimer's disease (AD) is the most common form of dementia in the elderly. Over 5 million individuals in the United States currently have AD and, as the average age of the population rises, so does the incidence of AD. Genetics plays an integral role in AD risk, but the mechanisms which trigger disease on a cellular level are still undergoing investigation. We recently identified a mutation in the Tetratricopeptide Repeat Domain 3 gene (TTC3) in 11 relatives diagnosed with AD. This rare DNA change is predicted to be damaging by five distinct computer models. Furthermore, evidence from other researchers have found that brains from deceased AD individuals had lower levels of TTC3 and that the gene is involved in neuronal growth. Therefore, it has been suggested that TTC3 could play a protective role against AD and that genetic changes which reduce TTC3 expression may contribute to AD risk. A series of experiments to better understand the effects of the genetic change that this lab identified by studying induced pluripotent stem cells (iPSC) created from three individuals with the TTC3 change and three non- demented controls without the TTC3 alteration was proposed. iPSCs can be differentiated into disease relevant cell types to recapitulate the disease progression. Genetic tools will, then, be used to introduce the single base pair TTC3 change into the control lines and, in a reciprocal experiment, revert the change back to normal in the AD cases. Both, the original and edited versions of all the stem cell lines, will be grown under conditions that induce them to become neurons, a relevant cell type to study AD. These neurons will be evaluated as they age for morphological changes in shape and connectivity, as well as, being tested for cellular changes in proteins related to AD including amyloid beta and tau. Lastly, RNA will be collected from the cells, in-depth sequencing will be performed and alterations in the regulation of other genes will be looked for. Brain tissue from four relatives with the same TTC3 alteration will be used for RNA sequencing to try to identify RNA changes at both early and late stages of disease. These results will be compared to hundreds of RNA profiles from unrelated AD cases and controls. Through these experiments, the aim is to determine if the TTC3 change results in AD specific consequences in neuronal cells and if correcting this genetic change can fix the cellular abnormalities. The hope is to reveal the role that TTC3 plays in AD pathology, as well as, gain a greater insight into how TTC3 acts in a similar or distinct manner from other causes of AD.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Casey Cook	Mayo Clinic Jacksonville	Evaluating the mechanism by which TauA152T modulates risk of tauopathy	Aggregation of the tau protein is a neuropathological hallmark of several neurodegenerative disorders classified as tauopathies, including Alzheimer's disease (AD). While mutations in the tau gene microtubule-associated protein tau (MAPT) are known to cause primary tauopathies, no MAPT mutations were linked to AD until the discovery of the A152T gene mutation, which acts as a risk factor for AD. In addition to modulating risk for AD, the A152T tau mutation also influences risk for dementia with Lewy bodies (DLB) and the spectrum of frontotemporal dementia disorders, including progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Therefore, understanding how the A152T mutation increases disease risk and identifying new genetic modifiers that impact the resulting phenotype in A152T mutation carriers could provide significant insight into the pathogenic role of tau in neurodegeneration. Compelling evidence that the A152T variant is associated with increased soluble hyperphosphorylated tau in human postmortem tissue from A152T carriers compared to noncarriers when controlling for disease severity has been collected. Consistent with this, expression of A152T-AAV in nontransgenic mice leads to increased accumulation of hyperphosphorylated tau species that also remains within the soluble fraction. Therefore, it is speculated that the A152T tau variant increases risk of tauopathy by modulating both tau hyperphosphorylation and solubility. Therefore, the current project will investigate the pattern of phospho-tau deposition throughout the brain in A152T carriers and noncarriers to determine how its presence coincides with neurodegeneration. In addition, it will be determined whether phosphorylation of tau is required for the toxicity of A152T in vivo. It is anticipated that by furthering the understanding of how A152T influences risk of tauopathy, the proposed studies will provide novel insight into mechanisms of tau toxicity in AD and other disorders.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Takahisa Kanekiyo	Mayo Clinic Jacksonville	APOE and cerebrovascular aging in Alzheimer's disease	Brain vessels play an essential role in maintaining cognitive functions by providing oxygen, nutrition and growth factors from the blood flow and by eliminating toxic molecules such as carbon dioxide from the brain. Alzheimer's disease (AD) is the most common type of dementia, which causes progressive memory loss in aged people. Many human studies have shown that brain vascular damage is strongly associated with the increased risk for AD. In fact, approximately 80% of AD patients have some extent of brain vascular injuries. While accumulation, aggregation and deposition of toxic amyloid-β (Aβ) peptides in the brain are key events in the pathogenesis of AD, brain vascular dysregulation is likely to precede the pathological event during the disease development. Since brain vessels critically mediate the elimination of Aβ from the brain, the disturbance of the pathway is predicted to induce brain Aβ accumulation. Impairments of brain blood supply and blood-brain barrier (BBB) integrity also cause neuronal damage, synaptic dysfunction, and white matter injuries, which eventually lead to the pathogenic condition referred to as vascular cognitive impairment and dementia. Importantly, aging is a critical factor that contributes to both brain vascular dysregulation and AD pathogenesis. Thus, the major goal of this project is to define molecular mechanisms underlying the relationship between aging and brain vascular dysfunctions using, both, cell and animal models, to explore the pathogenic pathways of AD. In general, aging is predicted to be caused by accumulation of senescent cells in the body. The increase of p16INK4a, which plays an important role in cell cycle regulation, is one of the central mechanisms triggering senescent phenotypes. Therefore, it is hypothesized that aging-related upregulation of p16INK4a in vascular cells disturbs the homeostasis of the brain vascular system and Aβ clearance resulting in AD development. Humans have three types of the apolipoprotein E (apoE) gene (APOE2, APOE3 and APOE4). APOE2 is protective against AD, but APOE4 is the strongest genetic risk factor for the disease. APOE genotypes are also critically involved in the compromised cognitive performance seen in the elderly, which includes mild cognitive impairment and vascular cognitive impairment. Furthermore, APOE4 also causes dysfunction of brain vascular system, including BBB breakdown and the reduction of small vessels. Thus, our proposal will have an emphasis on the effects of APOE4 on senescent phenotypes caused by p16INK4a induction in the brain vessels. To reach the stated goals, three specific aims are proposed. In aim 1, the impact of senescence and apoE isoforms on vascular cell properties and Aβ metabolism will be determined. In aim 2, senescence- and apoE isoformregulated cell type-specific pathways in brain vascular pericytes and endothelial cells will be defined. In aim 3, the examination of how the induction of p16INK4a in vascular mural cells and endothelial cells alter the amyloid pathology, the cerebrovascular system and the cognitive functions, depending on apoE isoforms. Collectively, these studies should provide novel insights into the cellular and molecular mechanisms that underlie the contribution of apoE and cerebrovascular aging to AD pathogenesis.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Feng Cheng	University of South Florida	System analysis of potential drug interactions in the treatment of Alzheimer's disease from theFDA reporting system, electronic health records and protein interaction networks	Some drugs have been used in the palliative care of Alzheimer's disease (AD) to treat some of the symptoms such as depression, anxiety and difficulty sleeping. However, these drugs may cause drug-drug interactions (DDIs). Recently, clinical studies showed that the AD patients are at an increased risk of DDIs. For example, combining cholinesterase inhibitors (such as tacrine, donepezil, galantamine, and rivastigmine) with some drugs could increase the risk of gastrointestinal disorders, bradycardia and loss of consciousness. In addition, an elderly patient with AD may have several medical conditions. The concurrent use of multiple drugs for other diseases among the AD patients has tremendously increased. The presence of multiple diseases may also impair the metabolism in elderly individuals, resulting in DDIs that are not common in healthy individuals. DDIs may have potentially life-threatening outcomes, especially for elderly patients. Therefore, AD patients should carefully evaluate the DDIs when prescription medication is used with other drugs and the detection of DDIs is an important field of AD patients' healthcare. The Food and Drug Administration (FDA) has routinely collected data on adverse drug events (ADEs) submitted to FDA and stored in the FDA Adverse Event Reporting System (FAERS) since 2004. The availability of real-world data from FAERS provides a rich opportunity to identify unexpected DDIs. However, FAERS contains approximately 7.5 million patient records, making it impossible to manually summarize all these records. Also, DDI information cannot be directly and accurately extracted from reports of patients who receive complex combinations of medications without using appropriate algorithms. It is difficult to identify real DDIs from the huge number of possible combinations of drugs and events. Therefore, in this proposal, the development and evaluation of an efficient computational model that can predict possible DDIs, especially from those records of AD patients in FAERS. The DDIs identified by the computational model will be validated through a retrospective analysis of electronic health records (EHRs) of AD patients. The mechanism of the DDIs will be explored by using drug-protein, protein-protein networks. The successful completion of this project will provide useful information for doctors to prescribe drugs for the palliative care for AD patients (Focus Area 1.3) more appropriately.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Joshua Gamsby	University of South Florida	Correction of Tauopathy-induced Circadian Dysfunction	Sleep is an essential part of a healthy lifestyle. Patients with Alzheimer's disease frequently report having trouble with sleep as part of their illness, which may worsen their other symptoms. However, why Alzheimer's patients have problems sleeping is poorly understood. This proposal is focused on uncovering how Alzheimer's disease impacts the region of the brain that is important for maintaining normal sleep timing, and on improving our understanding of how sleep disruption may contribute to the impaired memory of patients with Alzheimer's disease. It is also proposed that a new approach to treat this often overlooked, but extremely troublesome symptom. This work is hoped to improve the quality of life of patients suffering with Alzheimer's, as well as their caregivers, who must provide for them when they are wakeful.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Beniot Giasson	University of Florida	Understanding the molecular mechanisms of seeding and transmission of wild type and mutant tau	The accumulation of brain neuronal aggregates comprised of the protein tau is a defining hallmark of Alzheimer's disease (AD). The abundance and distribution of tau aggregates throughout the brain correlate with AD severity. The direct involvement of tau in disease has been unequivocally established by the discovery of tau mutations that results in progressive dementia. Several recent studies have indicated that the spread of tau aggregates within affected brain regions occurs by cell-to-cell transmission of small amounts of tau aggregates further inducing tau aggregation in neighboring cells. To further inform on the general molecular mechanisms influencing the aggregation and spread of tau pathology, it is proposed to explore the relative effects of wild-type and additional disease-associated mutants in cellular and animal models. Intriguingly, preliminary data generated in this laboratory identified a specific region within tau, which is influenced by several tau mutations, as an important determinant in regulating tau aggregation. The impact of this region and nearby putative tau protein modifications in regulating the aggregation of tau will be assessed, both, in cellular and animal model systems. Collectively, these studies will provide novel insights in the specific molecular mechanisms influencing the induction and spread of tau pathology and the pathogenic consequences associated with tau aggregation and specific changes in tau protein.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Claes Wahlstedt	University of Miami	Preclinical investigation of an optimized formulation of resveratrol, JOTROL, for Alzheimer's disease	The Alzheimer's Association estimates that someone in the United States of America develops Alzheimer's disease (AD) every 68 seconds and that the rate will increase to every 33 seconds by the year 2050. In Florida alone, the Department of Elder Affairs estimates that about 450,000 people currently live with AD – i.e, approximately 10% of US AD cases are in Florida. These are alarming statistics, since to date, all of the FDA-approved Alzheimer's disease (AD) treatments are palliative, at best, and do not target the main hallmark of the disease, beta-amyloid (Aβ) peptides that aggregate into amyloid plaques in the brain of patients and animal models. There is an enormous need for new therapeutic strategies. One of the drugs that has shown promise to date is resveratrol (RSV). Although it has been investigated for its potential use in AD for more than a decade using cell and animal models, only in December 2015 did a phase II randomized clinical trial present evidence that RSV is indeed beneficial to AD patients. Indeed, this study by the Alzheimer's Disease Cooperative Study group (ADCS) indicated that a high dose of resveratrol (up to 2 grams daily) has beneficial effects including positive alteration of amyloid biomarkers in cerebrospinal fluid. Such high doses are needed because of the poor bioavailability of resveratrol with a marked first pass effect and degradation in the liver. Unfortunately, such high doses will cause gastrointestinal and other dose limiting side effects. A new oral formulation of RSV, JOTROL, has been developed by a Florida-based company (Jupiter Orphan Therapeutics) and shows markedly higher bioavailability when compared to unformulated resveratrol will be studied. It is proposed to test JOTROL in AD animal models to evaluate its efficacy at both preventing and treating AD-like pathology at molecular and behavioral levels. Resveratrol has known epigenetic activity, including activation of the SIRT1 gene in the brain, which is likely to be more pronounced by equimolar doses of JOTROL. This group has successfully used AD animal models to test small epigenetic molecules in the past and anticipate obtaining positive effects with JOTROL in this project. A team of experts with vast experience in Alzheimer's disease, resveratrol chemistry and epigenetics has been assembled.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Suren Tatulian	University of Central Florida	Structure and Toxicity of Amyloid Beta Hetero-Oligomers	Alzheimer's disease (AD) is the major cause of dementia. To date, no effective therapies have been developed for the disease. Identification of novel biomarkers may facilitate development of efficient diagnostic and therapeutic strategies to combat AD. Amyloid beta (Abeta) peptide plays a major role in AD and occurs in various forms. While the most prevalent forms are the 40- and 42- amino acid residue peptides (Abeta1-40 and Abeta1-42), N-terminally truncated and pyroglutamylated Abeta peptides (AbetapE) constitute 10 to 50 % of total Abeta in AD brains, are hypertoxic, and augment Abeta cytotoxicity even at low molar fractions. The molecular mechanism of AbetapE hypertoxicity remains unknown. Currently, Abeta1-42 and Abeta1-40 are the major biomarkers targeted by AD immunotherapy trials, which have led to serious side effects such as meningoencephalitis, vasogenic edema, and brain microhemorrhages. Recently, a monoclonal antibody against AbetapE3-42 has been identified as a promising passive immunotherapy agent in mice. Further efforts towards identification and characterization of novel AD biomarkers, such as hypertoxic Abeta/AbetapE coaggregates, will likely lead to better, clinically acceptable AD immunotherapies. It has been recently identified that Abeta1-42 and AbetapE3-42 reciprocally inhibit fibrillogenesis and shift the aggregation process towards beta-hairpinlike structures stabilized by intramolecular Hydrogen bonding. Cell-based studies showed that Abeta1-42/AbetapE3-42 hetero-oligomers exerted the maximum toxic effect on neuronal PC12 cells as compared to oligomers of individual peptides or fibrils. Collectively, these findings support a novel concept that a) interaction between Abeta1- 42 and AbetapE3-42 inhibits fibrillogenesis and promotes formation of hetero-oligomers of unique structure and b) these hetero-oligomers, not Abeta1-42 or AbetapE3-42 oligomers, are the most cytotoxic species and, hence, constitute a novel biomarker to be targeted for efficient AD immunotherapies. Based on these findings, the hypothesis is that heterogeneous aggregates of different Abeta species, including AbetapE, exert the major neurotoxic effect in AD. Hence, the focus of basic and clinical studies should be shifted from individual Abeta species to hetero-oligomers. This project aims at detailed characterization of the structure and cytotoxicity of Abeta/AbetapE hetero-oligomers by pursuing the following specific aims. Aim 1: Identify the effect of AbetapE on Abetafibrillogenesis and accompanying structural transitions upon co-aggregation. The hypothesis that, contrary to the existing paradigm, AbetapE inhibits fibrillogenesis and promotes formation of hetero-oligomers with Abetapeptides will be tested by isotopeedited Fourier Transform Infrared (FTIR) anaylysis, fluorescence, atomic force microscopy and other biophysical and biochemical methods. Aim 2: Determine the critical morphological and atomic-resolution structural distinctions between aggregates formed by AbetapE alone and combined with unmodified Abeta. The hypothesis that AbetapE, Abeta and their mixtures undergo aggregation via distinct structural pathways will be tested at the morphological and atomic levels using advanced transmission electron microscopy and solid-state NMR. Aim 3: Determine the cytotoxicities of Abeta, AbetapE, and combined Abeta/AbetapE samples of defined aggregation states and structures. The hypothesis that Abeta/AbetapE hetero- oligomers possess maximum cytotoxicity as compared to Abeta or AbetapE oligomers or fibrillar peptide assemblies will be tested. A wider variety of heterogeneous systems, including other Abeta species such as 40- and 42-residue peptides, will be studied.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Antonio Barbosa, Ph.D.	Ave Maria University	Inhibiting Alzheimer's Disease by Modulating a Key Player in Plaque and Tangle Formation, SIRT1, by Regulating the Formation of Nicotinamide Metabolites	Alzheimer's disease (AD) is a devastating neurological disease that currently affects approximately 480,000 Floridians. While significant progress has been made to understand the protein pathology of AD, it is unclear why some individuals develop AD. Increasing evidence suggests that AD is linked to changes in the metabolic profiles of patients. Accordingly, specific metabolites may work to promote neuron survival. Therefore, we propose to investigate how the metabolite methyl-nicotinamide (Me-NAM) acts on the key metabolic protein sirtuin 1 (SIRT1) to promote neuron survival. To do this, we have established a multi-investigator team of researchers in biochemistry, medicinal chemistry, and biology to address the major grant priority area of novel therapeutic targets and strategies (Focus Area 2.1). SIRT1 is a deacetylase protein that prevents the formation of Tau tangles and amyloid beta plaque build- up in AD. Increasing SIRT1 activity has been shown to reduce these Tau tangles and amyloid beta plaque build-up in mouse models of AD. One metabolite byproduct of SIRT1 activation is nicotinamide, a component of the vitamin B3 complex. Nicotinamide is converted to methyl-nicotinamide (Me-NAM) by the Nicotinamide N-Methyltransferase (NNMT) protein in the cells. Me-NAM was once considered an inactive metabolite, but it was recently found to stabilize SIRT1 protein in model liver cells. We hypothesize that increased NNMT activity will increase Me-NAM levels and thereby directly enhance beneficial SIRT1 protein stability and activity in neurons. Our multi-investigator team of researchers will work closely with undergraduate biochemistry, chemistry and biology majors to study this hypothesis with three goals. First, we will investigate how Me-NAM stabilizes SIRT1, a mechanism that is currently not known. Second, we will explore a detection system for Me-NAM metabolites and NNMT activity. Finally, we will perform a small drug screen to identify chemical compounds that modulate NNMT activity and determine the effect of this increased NNMT activity on SIRT1 stability. We will use known SIRT1 activating compounds synthesized by our students as positive controls for our studies. We anticipate that this research will be beneficial for the discovery of new therapies for AD. Support from Ed and Ethel Moore Alzheimer's Disease Research Program would be tremendously useful for advancing these studies.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Jigar Modi, M.D., Ph.D.	Florida Atlantic University	Neuroprotection of GCSF Gene Therapy in Alzheimer's Disease	Alzheimer's disease (AD) is responsible for a major proportion of mortalities in the elderly. We have previously investigated novel mechanism-based therapies for stroke in cell culture models and in rodent disease models. Gene therapy offers unique opportunities for translational medicine by refining the products of defective genes in diseases and/or offering vital biologics from endogenous sources for tissue recovery processes. However, validating methods for the delivery, distribution and expression of the exogenous genes from such therapy can generally not be applicable to monitor effects over the long term because they are invasive. Most GCSF (Granulocyte Colony Stimulating Factor) gene stimulate production of GCSF protein, is a glycoprotein that stimulates production of granulocytes and stem cells. We have recently noted that it has neuroprotective properties as well as facilitation of stem cell differentiation. In 2016, we reported that human granulocyte colony-stimulating factor (hG-CSF) cDNA incorporated in scAAV-type 2 adeno-associated virus, as introduced through eye drops at multiple time points after cerebral ischemia utilizing bilateral carotid occlusion for 60 min (BCAO-60) resulted in substantial drop in mortality rates, cerebral atrophy, and neurological deficits in C57black6 mice. In application to AD, GCSF gene treatment has been found to improve the spatial learning performance and reduce amyloid depositions in the hippocampus and entorhinal cortex of mice animal models, however the mechanism of this interaction is still unclear. Given that AD is the 6th leading cause of death in United States of America, understanding the neuroprotective and neurogenesis mechanism of GCSF gene as a potential therapeutic agent for neurodegenerative diseases such as Parkinson's disease and AD is highly desirable. In our new studies addressing AD we propose that the GCSF gene treatment could serve as potential therapeutic agents for AD. We proposed that GCSF gene could be potential therapeutic agent for AD by first testing its effects in an in vitro setting as proof of concept. Preliminary results confirmed that cell survival rate of PC12 cells was significantly improved after exposure to A-Beta toxicity when compared to baseline values ($P < 0.05$) with GCSF gene intervention. In examining G-CSF gene treatment of PC12 cells exposed to A-Beta toxicity we demonstrated an increased survival rate in GCSF gene treated cells by comparison to control cells. In examining the therapeutic potential of GCSF gene in PC12 cells, was found to be neuroprotective against either glutamate induced toxicity, hypoxia/re-oxygenation. GCSF gene treatment also showed dose dependency action against A Beta over varying concentration of 20 pfu/cell and 40 pfu/cell. Overall, this is an indication that GCSF gene can in fact protect against A-Beta toxicity, a bio marker of AD. Our ongoing studies involve examining the neuroprotective potential of GCSF gene in vivo using rodent models of AD. We plan to further understand the mechanism and to determine effects of GCSF gene on cognitive functions using the animal model for AD.

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Yi Liao, PhD	Florida Institute of Technology	CO Releasing Polymer Nanoparticles for Treatment of Alzheimer's Disease	This is a pilot project aiming at development of a nanomedicine for Alzheimer's disease (AD). More than 35 million people worldwide suffer from AD including about 5.5 million Americans. Currently, there is no cure for AD. Although carbon monoxide (CO) is known as a toxic gas, it is actually naturally produced in small quantities and plays important roles in biological functions. Studies in the past two decades have shown many beneficial effects of CO. In fact, inhaled CO has entered clinical trials for treatment of inflammation and cardiovascular disorders. It was found that level of CO increased in the brains of AD patients. A later study showed that Heme oxygenase-1 produced CO to protect brain cells from damage caused by amyloid related to AD, which is consistent with the neuroprotecting effects of CO suggested by many studies. Since CO is toxic at high level, control over the dose of CO is important. Carbon monoxide releasing molecules (CORMs) have been studied in the past decade for controlled release of CO. Beneficial effects of a CORM on brain cells have been demonstrated by a in vitro study. However, there is no report showing that the CORM can pass blood-brain barrier. In this project, we will develop brain-delivery polymer nanoparticles loaded with CORMs, and study their CO releasing profile. These nanoparticles are expected to be able to release CO in the brains of AD patients, strengthen the self-protecting measures naturally adopted, and ease the symptoms of AD. The brain-delivery nanoparticle is based on polysorbate 80-coated polybutylcyanoacrylate nanoparticle, which has been widely used to deliver different drugs to brain. Two types of CORMs will be loaded to the nanoparticles. The first type of CORM releases CO through a hydrolysis mechanism. The second type releases CO upon photo-irradiation and thus can be selectively activated at the sites where amyloids are observed. Results of this pilot project will allow the therapeutic effects of CO on AD to be carefully studied and the related drugs to be developed in the future. The PI has extensive experience in CORM development and polymer chemistry, and thus is well qualified to conduct this project.

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Madhavan Nair, PhD	Florida International University	Therapeutic role of Withaferin A and CRID3 in the prevention of AD. A Novel Nanotechnology Approach.	Alzheimer's Disease (AD) is a growing threat to healthcare in the aging population and is marked by the accumulation of amyloid beta deposition in the brain and the pathology is enhanced by neuroinflammatroy process. Inflammasomes are recently known multiprotein signaling complexes and are known to trigger inflammatory proteins such as IL-1beta that is known to play a significant role in the genesis of AD. Among the inflammasome complexes, a nucleotide-binding oligomerization domain-like receptor, NLRP3 and nuclear factor kB (NFkB) are the major neuroinflammatory pathways that lead to AD. Therefore, therapeutic drugs which can target both NFkB and NLRP3 activation will play a major role in reducing amyloid beta levels and prevention of neuropathology of AD. In our preliminary studies, we have reported for the first time that Withaferin A (WA), an extract from Withania somnifera plant, known to inhibit NFkB activation, improved synaptic plasticity and neuronal spine density; and significantly inhibited amyloid beta production and amyloid beta induced neurodegeneration. Furthermore, we have also demonstrated that cytokine release inhibitory drug 3 (CRID3), an inhibitor of NLRP3 significantly prevented neuroinflammation in our in vitro model system. Therefore, use of these therapeutic drugs targeting both NFkB and NLRP3 will have a translational significance in the prevention of neuroinflammation and associated neurodegeneration in AD patients. However, these drugs are impenetrable to the brain to prevent neuroinflammation and subsequent neurodegeneration. The use of nanotechnology in medicine has exciting prospects for the development of a novel drug delivery system to the brain across the Blood Brain Barrier (BBB). Our recently described manuscript and atented technology (US20130317279 A1 and WO patent: CT/US2013/068698) that describes magnetoelectric nanoparticles (MENPs) as a novel drug carrier which offers unique capabilities including its low energy and dissipation-free on-demand drug release across BBB. Accordingly, we will use MENPs as a carrier molecules to deliver WA and CRID3 across BBB to inhibit the NFkB and NLRP3 mediated neurodegeneration in AD using our patented novel nanotechnology approach: Thus in the Aim # 1: we will investigate the effect of Withaferin A and CRID3 in inhibition of amyloid beta induced NFkB and NLRP3 activation, respectively and associated down-stream inhibition of pro-inflammatory cytokines and amyloid beta production in mixed in-vitro microglia and SH-APP (APP over expressing SH-SY5Y neuronal cell line) cell culture models. In Specific Aim # 2, we will develop and characterize MENP bound WA and CRID3 within the liposomes (to increase the drug stability, bioavailability and target specific brain delivery of these drugs); and study its non-invasive BBB transmigration, on-demand controlled release and therapeutic efficacy of the developed cargo using the in-vitro BBB model; while specific Aim # 3 will study the therapeutic efficacy (synaptic plasticity and neurobehavioral) of this novel nanoformulation in APP/PS1 AD mouse model.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Henry Carretta, PhD	Florida State University	Disparities in Health Services Utilization Across Racial/Ethnic Groups Among Persons with Alzheimer's Disease and Related Conditions	Alzheimer's disease (AD) is the most common form of dementia. It is a progression neurodevelopment disease associated with high morbidity and mortality. Some research suggests that risk factors for heart disease and stroke, e.g. high blood pressure and high cholesterol increase the risk of AD. Florida experiences an elevated population burden due to AD. Extant evidence suggests that there are significant disparities in prevalence, treatment and diagnosis rates, use of services, and mortality across racial and ethnic groups for AD and related disorders. The overall purpose of the project is to describe the prevalence, use of services, comorbid conditions and mortality across racial and ethnic groups with AD and related disorders and their relationship with known comorbid risk factors to provide fundamental insights for potentially modifiable risk factors. The project will help to define and quantify the nature and size of racial/ethnic differences and disparities in service utilization and access to care as the first step is establishing a blueprint for their resolution. We propose the following research questions (RQ) to more precisely parse the relative importance of various risk factors and to extend the national and regional findings to Florida. RQ 1: Is health services utilization (11 categories) among minority AD Medicare beneficiaries different from the majority white population? RQ 2: Are expressed difficulties in access-to-care among racial/ethnic minorities with AD different from the majority white population? RQ 3: Are the prevalence and mortality rates among racial/ethnic minorities with AD different from the majority white population? Methods: The Medicare Current Beneficiary Survey (MCBS-C&U) 2009-2012, is a continuous, multi-purpose survey of a representative sample (~12,000) of the Medicare population, including aged and disabled enrollees. The MCBS-C&U file is a combination of self-reported survey data and respondent Medicare claims summaries. Survey questions cover health status and function, health insurance, household and facility characteristics, demographics (detailed race and ethnicity categorization) and cost and utilization provided by their Medicare claims and self-report for inpatient, outpatient, prescription drugs and facility use among others. Detailed questions about activities of daily living, instrumental activities of daily living and caregiver status are also included as well as behavioral issues like substance abuse, exercise, diet and weight. Analysis: The analysis will estimate 11 measures of utilization e.g., inpatient, ambulatory, long term care, and prescription drug utilization, as well as across racial ethnic groups identified by the survey. Analysis will include cross-sectional analysis of each year as well as longitudinal analysis of the 2009 to 2011 data. Descriptive and predictive models will provide measures of racial/ethnic differences and to identify the relative importance of known risk factors. Study results will become the first step in a research agenda with the goal of conducting longitudinal access and utilization and disparities research using all Medicare beneficiaries across the time period 1999 to 2013. Since AD and related disorders often progresses slowly, long-term, life course studies that track persons before the first diagnosis with many years of follow-up are more likely to elucidate causal patterns of the identifies disparities.

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Melissa E. Murray, PhD	Mayo Clinic Jacksonville	Quantitative Neuropathology and Biochemistry of Survival Differences in Hispanic Americans with Alzheimer's Disease	Risk of developing Alzheimer's disease (AD) dementia is one-and-a-half times greater in Hispanic Americans compared to European Americans, and twice as high in African Americans. Intriguingly, Hispanic Americans are found to live longer with the disease, suggesting that there may be protective factors currently unknown. With one of the largest series of autopsy-confirmed Hispanic Americans having an AD neuropathologic diagnosis (n=85), we are uniquely positioned to examine what changes in the brain may account for differences in survival. Using sophisticated technology to measure AD-related changes to proteins, we will be able to examine what biological factors may differ between Hispanic Americans and European Americans. We will also provide exploratory comparisons with autopsy-confirmed African Americans with AD in a smaller cohort that is available (n=31). With a much larger cohort of European Americans (n=2651), we will be able to match case-to-case for important factors, such as age at death, sex, and education. We will carefully review clinical history for measures of cognitive reserve by examining evidence of bilingualism and converting occupation to a job level score (as recommended by the Department of Labor and Statistics). Together this data will provide one of the first translational neuropathology studies to specifically examine survival of Hispanic Americans with AD.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Chia-Chen Liu, PhD	Mayo Clinic Jacksonville	Impact of TREM2 Variants on Microglial Function and Alzheimer's Disease Pathology	Alzheimer's disease (AD) is a progressive neurodegenerative disorder with histopathological hallmarks of toxic amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain. However, targeting A alone has not yield a disease-modifying cure, suggesting a multifactorial and complex nature of disease etiology. Interestingly, genetic studies have uncovered multiple genes enriched in microglia, a cell type responsible for immune response in the brain, suggesting that microglia and related neuroinflammation are central to AD pathogenesis. Emerging evidence showed that microglial activation is a beneficial response in the early phases of AD, leading to increased Aβ clearance. However, at late stages of AD, microglia may paradoxically exacerbate the disease by secreting toxic pro-inflammatory cytokines in response to Aβ and other pathologies. Thus, understanding how microglia and neuroinflammation contribute to the disease development and progression may help determine the therapeutic window and strategy for introducing mechanism-based therapy for AD. Recent studies showed that a Arg-47-His (R47H) mutation of the triggering receptor expressed on myeloid cells 2 (TREM2) significantly increases AD risk by 3-4 fold. TREM2 is an innate immune receptor primarily expressed by microglia in the brain and is involved in inflammation and phagocytic clearance of Aβ and cellular debris. Although conflict data exist, TREM2 deficiency increases Aβ accumulation and neuronal loss in AD mouse models, suggesting that microglia may require TREM2 to respond to Aβ deposition and to limit neuronal damage. However, it remains unclear how AD-associated TREM2-R47H mutation affects microglial functions and amyloid development. We have recently developed novel mouse models expressing human TREM2 in an inducible, cell-type specific manner. After breeding to Cx3cr1-CreER mice, we generated microglia-specific TREM2 or TREM2-R47H mouse models in the Trem2-/- background. Using this unique model, we aim to dissect how expression of TREM2 and TREM2- R47H variant in microglia at different stages of amyloid pathology impacts cognition and amyloid pathogenesis. We hypothesize that the AD-associated mutation, TREM2-R47H, impairs microglial functions, enhances pro-inflammatory responses and exacerbates amyloid pathogenesis, thus accelerating AD pathogenesis. We also established several innovative approaches, including in vivo two-photon microscopic imaging (for examining the microglial responses and amyloid development), and in vivo microdialysis (for measuring brain ISF Aβ and inflammatory cytokines) for this proposed study. In Aim 1, we will determine the effect of microglial TREM2 and TREM2-R47H on inflammatory responses, neuronal functions and behaviors. In Aim 2, we will induce the expression of TREM2 or TREM2-R47H in the background of amyloid model mice at different stages of amyloid development to examine their effects on brain Aβ metabolism, amyloid pathology, and Aβ-associated microglia activation. Effects on brain Aβ clearance and neuroinflammatory cytokines will be assessed by in vivo microdialysis, whereas effects on amyloid plaque and microglial responses will be examined by histopathological, microscopical, and biochemical methods. Together, our proposed studies aimed at dissecting how TREM2-R47H modulates microglial functions and amyloid development should provide mechanistic guidelines as to how microglia-mediated neuroinflammation can be targeted in AD therapy.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
John A. Lucas, PhD	Mayo Clinic Jacksonville	Evaluating the Impact of a Dementia-Caring Community Model on African Americans with Alzheimer's Disease and Their Care Partners	Communities can play an important role in helping residents with Alzheimer's disease (AD) and their care partners obtain appropriate services and overcome the challenges and stigma that threaten quality of life, social well-being, and functional independence. Ethnic minority communities experience a disproportionately high degree of AD-related health disparities, including greater unmet needs and increased barriers to dementia information and health care. African Americans in particular have a significantly higher prevalence of AD than Caucasians but typically do not seek evaluation until much later in the disease course. A number of sociocultural factors contribute to this disparity, including lack of awareness of the early signs of AD, mistrust of the medical establishment, and limited access to clinical resources and caregiver support. The national plan to address AD encourages community engagement through the Dementia Friendly America (DFA) initiative of the National Alzheimer's Project Act (NAPA). This initiative provides a roadmap and tools to help systematically identify and implement opportunities to build dementia-caring communities, where residents, businesses, and local governments work together to be supportive and inclusive of people with dementia in the places they live, socialize, worship, and work. To date, these efforts have been implemented in 36 US cities across 28 states. In Florida, the Department of Elder Affairs supports DFA goals through the Dementia Care and Cure Initiative (DCCI), which began implementation in Leon County in 2016. Although a number of these efforts have engaged in program evaluations, there are currently no scientific studies documenting the objective impact of these efforts on important outcomes such as community AD awareness, access to AD resources, or quality of life of people with AD and their care partners. Moreover, to our knowledge the DFA roadmap has yet to be implemented in a majority-African American community. Given sociocultural influences and the significant resources required to implement the dementia-caring roadmap, it is important to demonstrate objectively that these initiatives provide meaningful and measurable benefit. The aims of this proposal are to measure the impact of the dementia-caring community model on AD awareness, resource utilization, and quality of life in a traditionally underserved African American community in Jacksonville, FL. We expect that the findings from this study will help inform all communities about the potential scope and magnitude of outcomes of dementia-caring initiatives, assist ethnic minority communities in decision-making on resource allocation for such initiatives, and facilitate implementation of dementia caring programs in other ethnic minority neighborhoods across Florida.

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Heather Melrose, PhD	Mayo Clinic Jacksonville	Targeting Lrrk2 Activity to Modulate Tau Pathology	The link between leucine rich repeat kinase (LRRK2) and Alzheimer's disease (AD) pathology is intriguing. Brains with LRRK2 mutations can display pleomorphic pathology including tau and amyloid inclusions. Novel tau epitopes phosphorylated by LRRK2, and overexpression of human wild-type LRRK2 in mice promotes tauopathy. Several Rab GTPases, including Rab3, have been identified as in vivo LRRK2 substrates. Expression changes of Rab proteins and their effectors are found in post-mortem AD brain and effector rab3- GEF was recently nominated a modifier of tau toxicity in a genome-wide association meta-analysis for AD. It is proposed that overactive LRRK2 disturbs intracellular trafficking via promoting the dissociation of GDIs (guanine dissociation inhibitors) in the cytosol with concomitant membrane insertion, altering the relative pool of membrane bound and cytosolic Rabs. We suspect in unsuccessful aging in humans, the cellular localization of LRRK2 gradually alters and this increases the likelihood of this unwanted action of LRRK2.To examine the relationship between LRRK2 and tau, we expressed AAV-human tau on a LRRK2 G2019S mutant, knockout (KO) or wild-type background. Loss of LRRK2 increased survival of AAV-tau mice, despite reaching the same stage of Ab39- positive mature tangle pathology as the G2019S or WT mice expressing AAV-tau. Surprisingly, KO/tau mice had significantly more soluble phospho-tau than G2019S/tau or WT/tau mice, suggesting an alternative species of tau is the toxic mediator. We suspect that LRRK2 activity may have an unsolicited role in the spread of tau oligomers via rab protein signal regulation. Interestingly, it has recently been shown that worms expressing tau A152T mutant, a risk factor for fronto-temporal dementia, have cargo transport deficits associated with mislocalized Rab3a.We hypothesize that reducing LRRK2 levels will restore the Rab pool distribution and reduce abnormal trafficking of tau. LRRK2 is an attractive drug target, bearing a dual enzymatic core consisting of a kinase and GTPase domain. Drug companies have invested heavily in LRRK2 therapeutic programs and it envisaged that LRRK2 therapy could extend to neurodegenerative diseases like AD. As well as targeting enzymatic activity, there is also precedence for lowering LRRK2 levels. For example, LRRK2 silencing in rodents protects against inflammatory brain insult via lipopolysaccharide and α-synuclein-induced dopaminergic degeneration. For this proposal, we will test the effect of a LRRK2 inhibitor MLi2 (Merck) and a LRRK2 antisense oligonucleotide (ASOs, Ionis) in a mouse model of tauopathy that expresses low levels of human wild-type tau and in adulthood has tau seeding initiated via inoculation of tau filaments isolated from AD brain. Outcome measures in mice will be behavior, neuropathology and biochemistry. If successful, this work will underline a role of LRRK2 in AD with a focus on regulating intracellular trafficking and Rab GTPase biology. We hope to define early molecular changes related to tau spreading and which of these alterations might be reversible. Data to support a beneficial role of LRRK2 modulation in AD mouse models may also nominate biomarkers for disease diagnosis and progression/reversal monitoring.

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Mark T.W. Ebbert, PhD	Mayo Clinic Jacksonville	Identifying Drug Targets Using Long-Read Sequencing in Alzheimer's Diseased and Control Brain Tissue	Alzheimer's disease is remarkably complex and requires researchers to expand into new approaches to understand the underlying etiology. Large research efforts, including the International Genomics of Alzheimer's Project, have identified the top genes driving Alzheimer's disease status, and our group seeks to identify what is happening at the DNA and RNA levels within these top genes that drives disease development. We will perform deep, targeted long-read RNA isoform sequencing (IsoSeq) and long-read DNA sequencing in the lateral entorhinal cortex across Alzheimer's disease cases and controls, using Pacific Biosciences (PacBio) long-read technology, to identify problematic RNA isoforms and structural DNA mutations. Isoforms are different RNA transcripts from the same gene, while structural mutations are large segments of DNA that have been modified. PacBio's sequencing technology is the ideal technology to identify structural mutations and discern individual RNA isoforms. Our approach will enable us to identify disease-causing structural mutations and aberrant RNA isoforms driving both disease development and progression. Our approach provides a clear path to understanding a crucial aspect of Alzheimer's disease etiology by identifying structural mutations that may be the functional mutations associated with genome-wide association hits researchers have been looking for. By studying the lateral entorhinal cortex, where pathogenesis typically begins, we can maximize the likelihood of finding any mutations involved in disease, ultimately leading to effective therapeutics. It is critical that we study top genes in the diseased tissue, because genetic mosaicism is evident across tissues. Dr. Ebbert has the required experience in Alzheimer's disease research, next-generation sequencing technologies, algorithm development, and advanced analysis techniques to carry out the aims outlined in this proposal. Importantly, Dr. Ebbert is joined and supported by top experts in the field, including Dr. John Fryer, an accomplished molecular biologist, Dr. Dennis Dickson, a renowned neuropathologist, and collaborators at Integrated DNA Technologies (IDT) and Pacific Biosciences, who are experts in targeted long-read sequencing. We are confident existing evidence supports our aims and that this project will impact Alzheimer's disease research.

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Sindy Goenaga, MD	Mount Sinai Medical Center	Impact of the Modified MindSet Training Program on Maintaining Optimal Function Among Early Alzheimer's Patients and Their Care Partners	The Wien Center for Alzheimer's Disease and Memory Disorders seeks a pilot grant of $100,000 from the Ed and Ethel Moore Alzheimer's Disease Research Program to support implementation and to assess the impact of a novel modification of the Mindset Training Program. This project is very much aligned with the goals of the Florida Department of Elder Affairs Alzheimer's Disease Initiative and its Dementia Care and Cure Initiative. This program will address Priority Area 1 as described in the Funding Opportunity Announcement. The project will particularly address focus area 1.2 which is the social environment of persons with Alzheimer's disease and related dementia (ADRD), and focus area 5.3 as it addresses novel diagnostic procedures, tools, and strategies. The aims of the novel project are: (1) to implement the Revised MindSet Training Program, (2) to assess and measure the following outcomes: overall satisfaction with this training program, effects of the program on communication between the care recipient and their care partner, effects of the program on patient cognition and function in both English and Spanish speaking individuals. This pilot program will be implemented over the next two years and will target persons with Mild Cognitive Impairment (MCI) and early stage dementia. The MindSet training program was originally developed as a 6-week course, based upon a study program conducted by Dr. David Lowenstein at the University of Miami. The curriculum was developed to be used in small groups in a classroom format, with an emphasis on participants will learn exercises to better maintain their functional abilities and to develop strategies to better use the cognitive skills they currently possess. In this proposal, there will be an increased focus on improving attention, enhancing cognitive processing speed, spaced retrieval, procedural memory, and other techniques that engage cognitive functions which are not greatly dependent on memory. Further, there will be efforts to assist the care provider with enhanced communication skills, stress management techniques and behavioral skills that should optimize quality of life for both the caregiver recipient and care provider, enhance communication skills and strengthen the caregiver and care recipient partnership. This novel project will provide persons with MCI and early stage dementia with tools which will allow them to maintain or prolong independence and functionality as well as a means to build social support networks and improve communication and to increase quality of life. A unique aspect of this program as compared to the original Mindset program is a dual focus on both care recipients and care providers in supportive small group settings. It is expected that the caregivers or study partners of the participants will also benefit from this training program by allowing them to be active agents in improving the quality of life of the patients and to reduce caregiver stress.

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Ken Teter, PhD	University of Central Florida	Protein Disulfide Isomerase Uses Conditional Disorder as a Disaggregase Mechanism to Detoxify Amyloid Beta Fibrils	In Alzheimer's Disease, neurotoxic aggregates of Aβ peptide damage the brain. Protein disulfide isomerase (PDI), which is produced by most cells in the human body, can prevent the aggregation of Aβ. An S-nitrosylated form of PDI that cannot prevent protein aggregation is found in the brains of individuals with Alzheimer's Disease. PDI has also been found embedded in aggregated Aβ plaques. Our recent studies have identified a novel property of PDI that could be linked to its protective role in Alzheimer's Disease. We have shown PDI will unfold upon contact with aggregated Aβ, which provides a possible molecular mechanism for the disruption of protein aggregation by PDI: unfolded proteins are larger than folded variants of the same protein, so the expanded size of unfolded PDI would push against two peptides in the Aβ aggregate and consequently act as a wedge to displace individual peptides from the aggregate. PDI could thus reverse, as well as prevent, Aβ aggregation. In support of this model, we have shown PDI can dissolve neurotoxic aggregates of α-synuclein, a protein that contributes to Parkinson's Disease. Preliminary data indicate PDI can also protect neuronal cells from the toxicity of aggregated Aβ. For our project, we will define the structural events that accompany the Aβ-induced unfolding of PDI and its resulting disaggregase activity that dissolves and detoxifies amyloid fibrils. This work will provide detailed mechanistic insight into the unique and previously unrecognized disaggregase activity of PDI that could identify recombinant PDI as a potential treatment for amyloid-induced neurodegeneration.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Florencio Hernandez, PhD	University of Central Florida	Optical Characterization of the Aggregation (Change in size, Fibril Formation), Accompanying Structural Changes, and Membrane Pore Formation	Alzheimer's disease (AD), the most common form of dementia in senior citizens is among the top six leading causes of death in the USA, and the number of cases is projected to triple by 2050. Because of its irreversibility, AD poses a large financial and social burden in families and society. Therefore, finding ways to prevent, stop the progression and cure AD is a vital priority. For this purpose a better understanding of the pathophysiology of AD need to be achieved. It is currently known that AD is characterized by the extracellular deposition of amyloid plaques in the cerebral neuropil and vasculature, and the accumulation of intracellular neurofibrillary tangles. However, there is not solid consensus on the species of amyloid peptides (A) that exert the major neurotoxic effect, e.g. while the original amyloid hypothesis suggested that the degree of accumulation of insoluble fibrils of amyloid determines the extent of neurotoxicity, recent evidence support the role of soluble amyloid peptides and oligomer aggregates as the main neurotoxic effectors. In addition, besides the aggregates size, the cytotoxic effect of A seems to be determined by its molecular conformation. However, more fundamental structural studies are needed to establish a better correlation between the specific structural characteristics of A and their neurotoxic effect. Here we propose a novel approach for the structural analysis of different species of A that will lead to a better understanding of the process of A aggregation and fibrillation, and membrane pore formation potentially involved in AD. Throughout this project we will combine twophoton circular dichroism (TPCD) and isotopeedited FTIR (IE-FTIR) to tackle the structural distortions underlying the aggregation of full-length A and several fragments that represent structurally distinct and functionally important stretches of the peptide. The high sensitivity of TPCD to small structural distortions and its capability to access specific conformational fingerprints in a region of the electromagnetic spectrum inaccessible by any other means (VUV), synergistically working with the characteristic site-specific resolution and sensitivity of IE-FTIR to small differences in intra- and interstrand H-bonding in -sheets, guarantee the access to specific conformations and structural distortions of specific peptide oligomers (A11-28, A25-35 and A1-42) that can result in the formation of amyloid plaque seeds. This approach will overcome some of the limitations presented by the techniques most commonly used for structural analysis. The findings of the proposed research will have a strong impact on fundamental research of D.

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Amy Donley, PhD	University of Central Florida	Factors Influencing Family Caregivers' Medical Decision-Making for Patients with Advanced Alzheimer's Disease	Advanced Alzheimer's Disease (AD) is characterized by severe cognitive and functional impairment that necessitates family caregiver involvement in medical decision-making as patient surrogate decision-maker. Caregiver choices to seek, accept, or discontinue medical treatments greatly influence quality of life, utilization of health care services, and length of patient survival. Little is known, however, about how they come to these decisions. This study will examine factors that influence family caregivers' medical decision making in the context of advanced AD. The naturalistic decision-making model that focuses on the role of personal and situational factors in making decisions, will provide a conceptual framework for the study. A sample of 20 family caregivers for 20 homedwelling patients with advanced AD will be will be recruited from the Centre for Senior Health. Data will be collected in qualitative semi-structured interviews every four months for up to 12 months. The interview schedule will address 1) medical events that occurred in the past four months; 2) medical decisions made by family caregivers in response to these events; 3) influence of health care professionals and lay persons on caregivers?decisions; 4) role of situational factors in caregivers? decisions (e.g., access to health care services, financial resources), and 5) caregiver satisfaction with their decision outcomes. All interviews will be audiotaped, transcribed, and analyzed using grounded theory methodology. Knowledge gained through this study will inform educational strategies and supportive interventions to improve family caregivers' medical decisionmaking in the context of home-based management of advanced AD. By highlighting the role of family caregiver in the medical management of advanced AD at home, the study will contribute to a paradigm shift in the health care system approach to family caregivers being seen primarily as passive victims of caregiving stress to active participants in the care process.

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Lakshmyya Kesavalu, BVSc, MSc, SCC	University of Florida	Periodontal Bacteria Augment Progression of Abeta; and Tau Pathology	Alzheimer's disease is a progressive loss of memory in which individuals experience memory decline that begin gradually and gradually worsen. Alzheimer's disease occurs in senior citizens aged 65 and above, but memory loss symptoms can develop in individuals in their 40 years and 50 years. Furthermore, memory loss, other symptoms include strong anxiety, loss of control of movement and the loss of the ability to communicate coherently and sleep difficulties. Alzheimer's disease is a complex disease and we do not know what causes with both environmental and genetic risk factors, contributing to its onset. There is no cure for Alzheimer's disease. The brains of Alzheimer's patients commonly contain nerve cell abnormalities called as plaques or tangles. Several epidemiological, clinical and molecular studies have shown that chronic gum disease in the mouth associated gum swelling and redness (co-morbidity or cofactor) is linked with increased risk and progression of varying forms of memory loss, including Alzheimer's disease. Gum disease are among the most common chronic infections of humans, characterized by loss of tooth supporting gingival tissues and caused my complex bacteria underneath the gums. Numerous studies link gum disease associated chronic inflammation with increased risk of dementia, including Alzheimer's disease. Plasma levels of antibodies to gum disease bacteria are significantly higher in Alzheimer's disease patients. One study directly showed the presence of 7 different gum disease bacteria (Treponema denticola, Treponema pectinovorum, Treponema socranskii, Treponema vincentii, Treponema maltophilum, Treponema amylovorum, Treponema medium) in Alzheimer's diseases patient's brains. We also observed oral bacteria component present in 4 out of 10 Alzheimer's disease brains. We do not know the mechanism by which gum disease may be considered a risk factor for Alzheimer's disease. To best of our knowledge, there is no study examined gum disease bacteria could damage brain nerve in susceptible genetic mouse model of Alzheimer's disease. We hypothesize that gum disease bacteria can cause increased brain nerve damage. The specific aims are to explore the gum disease bacteria T. denticola infection in regulating brain nerve damage in TgCRND8 mouse model. The objective is to determine the possible causal association between gum disease bacteria with Alzheimer's disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Paramita Chakrabarty, PhD	University of Florida	Towards Understanding the Biological Role of Newly Discovered Alzheimer's Disease Susceptibility Genes Affecting Immune Function	Towards Understanding the Biological Role of Newly Discovered Alzheimer's Disease Susceptibility Genes Affecting Immune Function Gliosis, reflective of the underlying alterations in microglial function, is a pathological feature of Alzheimer's disease. Recent genetic and transcriptomic data have identified several microglial genes that are part of an innate immune network that is associated with increased risk of Alzheimer's disease. Cumulatively, gene expression data from various laboratories, including ours, suggests that altered immune response observed in Alzheimer's disease may have a direct role in the pathogenesis of amyloid β plaques and tau tangles, two hallmark pathologies in Alzheimer's disease. Indeed, our group, as part of the NIH AMD-AD consortium, has recently identified coding variants of two novel microglia-specific genes, ABI3 and PLCG2, that confer significant risk for Alzheimer's disease. The ABI3 gene variant (rs616338: p.Ser209Phe) increases the risk for Alzheimer's disease where the PLCG2 variant (rs72824905:p.Pro522Arg) is a protective variant. Protein-protein network analysis places both ABI3 and PLCG2 in an immune network encompassing two other Alzheimer's related microglial genes, TREM2 and SPI1. This strongly suggests a functional role for both ABI3 and PLCG2 in the Alzheimer's pathological cascade. However, the exact biological mechanisms underlying ABI3 and PLCG2 mediated events that alter microglia function and Alzheimer's pathogenesis is unknown. In this proposal, we have devised experiments that will help us understand the role of these two novel genes, ABI3 and PLCG2, in Alzheimer's disease pathological cascade. We will first generate mouse models of Alzheimer type amyloidosis that is deficient in either ABI3 or PLCG2 to assess how these genes affect Alzheimer-related Neuropathologies. Further using primary microglial cultures or brain slice cultures generated from different mouse lines, we will investigate how deficiency of ABI3 or PLCG2 proteins or overexpression of Alzheimer-associated variants of ABI3 and PLCG2 proteins affect amyloid β catabolism. Knowledge from this can help us understand how microglia-mediated immune response contributes to Alzheimer's disease pathogenesis and further will help in designing the next generation immune-therapeutics that can be used effectively as therapies in Alzheimer's disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Linda B. Cottler, PhD, MPH, FACE	University of Florida	Precision Public Health Approaches to Reduce Disparities in Memory Disorder Screening in Rural Minority Communities	Reducing health disparities for Alzheimer's Disease (AD) in mortality among Florida's diverse, aging, population is the focus of this proposal. Specifically, it will overcome barriers to accessing Florida's Memory Disorder Clinics. These barriers are especially relevant to rural and African-American populations 60 years of age and older in areas with the highest AD age-adjusted death rates in Florida. Barriers include: poor access to care, which complicates AD screening, diagnosis and treatment. Other barriers are at the community level (lack of public awareness), service provider level (insufficient specialty care, reluctance to diagnose, and inadequate capacity to screen) and individual and family levels (stigma, embarrassment, expensive treatment, a perception that care is ineffective and difficult to access, lack of knowledge about where to seek help, and denial). Building on our successful and innovative community engagement model called Health Street, we will empower Community Health Workers (CHWs), at the center of our model, to reduce these barriers. While the geographical areas we are focusing on have had the highest AD mortality rates, they have had the lowest AD case rates, suggesting a critical lack of screening. A key reason for this is lack of knowledge and misperceptions of primary care physicians on consequences of undiagnosed and untreated AD and how to refer to Memory Disorders Clinics. For this proposal, residents from 8 North and North Central Florida counties (population = 1,013,693; 193k >65 y/o) with the highest mortality from AD with one comparison site (Alachua) will be recruited: Bay, Calhoun, Franklin, Gulf, Holmes, Jackson, Liberty, Marion, Putnam, Wakulla and Washington). From 12 to 100% of these counties is rural; from 8% to 28% is African-American. From 14% to 29% are below the poverty level. Specifically, CHWs will assess 2,000 community members 60 years of age and older for cognitive status, Alzheimer's Disease knowledge, risk factors, social determinants of health and health histories; they will then be screened in the community with the Montreal Cognitive Assessment (MoCA). Based on their health concerns and needs, residents will be referred to medical and social services and be given referrals to further cognitive screening through their physician. The physician will be given educational materials on how to refer their patient to a local Florida Memory Disorder Clinic. CHWs will follow up with each person at 60 and 120 days to evaluate these metrics of success: screening referral, completion of screening, barriers, and increased knowledge of AD resources, consequences and symptoms among at risk community members, their physicians and caregivers. The main focus of this project is to improve recognition of AD in counties with large discrepancies between AD mortality and AD case rate.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Anthony T. Yachnis, MD	University of Florida	Investigations of Neuropathologies Targeted by Clinical Trials in Alzheimer's Disease Patients	Patients with Alzheimer's disease suffer from accumulation of pathological proteins including ABeta- amyloid and tau. These abnormal proteins are components of senile plaques and neurofibrillary tangles, respectively, which are the defining neuropathological findings in the disease. Many patients with Alzheimer's disease also have ABeta-amyloid accumulation in brain blood vessels, which predisposes them to hemorrhage or stroke. Multiple recent clinical trials have employed drugs that target Abeta- amyloid and tau, in order to inhibit or reduce accumulation of the abnormal proteins and curtail disease progression. In order to provide new insights in the contribution of specific Alzheimer's disease pathological proteins and how these are altered by specific therapeutic targets, we propose to uniquely assess the brain pathologies from patients that been the subjects of novel therapeutic treatments primarily at the Compass Clinic, Orlando. Compass has been involved in over 245 neurological trials in all phases and has enrolled over 10,000 participants in neurology alone. These patients will be extensively assessed for pathological findings using consensus guidelines from the National Institute of Aging/Alzheimer's Association, as well as novel state-of-the-art reagents and tools developed by the 1Florida Alzheimer's Disease Research Center (1Florida ADRC). This research will provide new insights into the effects of these therapies on ABeta or tau accumulation, while providing information on the relative role of specific brain pathologies driving the etiology of Alzheimer's disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Wolfgang Streit, PhD	University of Florida	Role of Microglia in Primary Age Related Tauopathy and in Sporadic (late-onset) Alzheimer's Disease	The most common form of Alzheimer's Disease (AD) accounting for more than 95% of all cases is called sporadic or late-onset AD (LOAD). Sporadic means that there are no clearly identifiable genetic abnormalities associated with it, and the disease can therefore affect anyone. Not only does it remain unknown why some people are more likely to develop LOAD, it is not even known or agreed upon by neuroscientists how exactly the disease evolves in an individual, i.e. the pathogenesis is incompletely understood. Obviously, an understanding of pathogenesis is essential for developing effective treatments. The best way to study LOAD pathogenesis is in human brains because LOAD is a uniquely human condition that laboratory animals cannot represent. Neuropathological studies have shown that the microscopic disease process, characterized by distinct lesions, begins as early as childhood and continues to gradually progress over subsequent decades until it eventually turns into LOAD. During much of this time, and as the microscopic pathology slowly worsens, individuals do not experience any problems with memory or cognition: clinically, they are considered normal (non-demented). If any of these individuals come to autopsy at this stage, a diagnosis of preclinical Alzheimer's can be made only after a neuropathologist has studied the brain and has found the characteristic lesions. However, it is still unknown at what point the pathologic changes in the brain have progressed sufficiently to cause clinical problems; in other words, how much pathology does it take to produce symptoms? The answer to that question means a better understanding of the disease process and therefore being able to devise effective treatments. We propose here to perform neuropathological studies on a random sample of thirty individuals who at the time of their deaths were non-demented. For each individual, we will examine the same brain regions (entorhinal cortex, hippocampus) identifying lesions that are characteristic of LOAD. We will use 5-6 specialized histological (immunohistochemical) procedures that will allow us to identify clearly Alzheimer- type lesions. We will pay particular attention to cells that make up the brain's immune system (microglial cells), as we, and others believe that microglia are critically important for the LOAD process. We expect that by examining in thirty individuals all of the three pathological hallmark features that are currently recognized to be important for understanding LOAD pathogenesis (plaques, tangles, and microglial activation), we will be able to significantly illuminate the chain of microscopic events that eventually results in dementia.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Guilian Xu, PhD	University of Florida	Seeded Interactions of Abeta; and Neurofibrillary Tangle Pathologies in Mouse Models	Although many transgenic mouse models exist that develop senile Aβ plaques and neurofibrillary tangles, it is not clear that any of the existing models show robust interdependency in which Aβ pathology influences tau inclusion formation. There have been multiple recent studies indicating that both Aβ and tau pathology can be independently accelerated in these models by injecting tissue preparations that contain high levels of misfolded Aβ or tau, respectively. These acceleration models produce animals in which pathology develops within 6 months of injection, or less, instead of taking 12 months or more. For example, we recently developed such a model system based on mice that express humanized amyloid precursor proteins encoding mutations linked to early onset Alzheimer's Disease (AD; APPswe/ind). These mice, termed PrP.APPsi express the transgene at a level that causes amyloid deposition beginning at 12-14 months. When human AD brain lysates are injected into the brains of newborn (postnatal day 0) PrP.APPsi mouse pups (P0 injection), we dramatically accelerate Aβ deposition such that a 12-month-old injected mouse had the level of amyloid pathology observed in 20-month-old uninjected mice. Thus far we have observed this outcome using inocula from several independent human AD cases. Similarly, Aβ deposition can also be dramatically accelerated by injecting brain homogenates prepared from transgenic mice with Aβ aggregates that express either human or mouse Aβ. A similar phenomenon is observed using mice overexpressing the P301S mutation of human tau and driven by the mouse PrP promoter (PS19), which develop spinal cord pathology beginning ~ 6 months of age and succumb to paralysis between 8-12 months of age. Numerous studies have demonstrated that intracerebral injections into PS19 mice with in vitro synthesized tau fibrils, or mouse and human lysates containing tau inclusions, can induce the earlier formation of neurofibrillary tangles. Together, these data demonstrate the ability for exogenously applied preparations of both Aβ and tau to enhance and accelerate the disease process in these transgenic mouse models. In the current proposed study, we hypothesize that seeding double transgenic mice expressing both human APP and P301S tau with inoculum containing one or both of these proteins will establish an accelerated mouse model that develops both Aβ plaques and neurofibrillary tangles before 6 months of age. If successful, such a model would be very useful in pre-clinical studies to identify therapies that slow the formation of Aβ and tau pathology.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Rosie Curiel, PsyD	University of Miami	Postdoctoral Fellowship in Neurophychology	The focus of the research fellowship application is to offer a promising postdoctoral candidate the opportunity to receive specialty training and develop skills in research methodologies used to clinically assess diverse older adults and individuals on the Alzheimer's disease continuum. Drs. Curiel and Loewenstein, who would serve as primary and secondary mentors at the University of Miami Center on Aging, have expanded their program of research that will host the training for the postdoctoral fellow. This training environment includes an ongoing longitudinal NIH RO1 on aging and cognition (Loewenstein-PI), and a new RO1 (Curiel-PI) which easily achieved the NIH pay line and focuses on state-of-the-art computerized assessment for the detection of preclinical AD. Moreover, our team also has two ongoing Ed and Ethel Moore research studies and leads a major scientific project at the 1Florida ADRC at Mt. Sinai Medical Center and provides all neuropsychological assessments for the UM Memory Disorders Clinic. Postdoctoral training also offers a strong focus on cross-cultural neuropsychological assessment and the development of culturally fair diagnostic assessment instruments, which is of critical relevance in the State of Florida. Taken together, this focused and highly productive program of research led by Drs. Curiel and Loewenstein, along with their longstanding background in academic training, serve to offer prime training opportunities for the postdoctoral candidate to expand their competency to serve minority older adults who are at risk for the development of neurodegenerative conditions such as AD. We are the only academic medical center in south Florida that can offer a postdoctoral research fellow the platform to cross-train on multiple Alzheimer's disease federally funded research studies at the UM Center on Aging. This, along with our collaboration with the 1Florida Alzheimer's Disease Research Center, would offer an unparalleled specialty training opportunity. Competent cognitive assessment that is sensitive to detect Pre-Clinical 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 our 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. Finally, the fellow will receive training in writing federally funded grants to prepare him/her to become an independent investigator. It is also relevant to note that our group has successfully and continuously trained Ed and Ethel Moore Postdoctoral Fellowship scholars since the program was initiated during the 2015-2016 year.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Noam Alperin, PhD	University of Miami	Cardiovascular and Lifestyle Stressors of Hippocampus and AD Related Brain Regions	Accelerated loss of brain tissue, especially in regions within the medial temporal lobe, is already apparent in preclinical AD. We aim to better understand how and why these cognitively critical regions are affected by external stressors. Our multidisciplinary team have a unique track record in novel cognitive stress testing for early detection of AD and in neuroimaging using quantitation of brain structures and hemodynamics. Our team has a productive collaboration on an NIH R01 study (PI Loewenstein) that focuses on early cognitive and biological markers of preclinical AD. We have completed recruitment and MRIs for nearly 250 community-dwelling older adults ages 60-90. Our project will take advantage of this tremendous resource to measure the magnitude of cardiovascular and lifestyle stressors and their impact on AD-vulnerable brain regions. The MRI protocol included 2 novel methodologies that will provide a more refined brain parcelation (e.g., hippocampus sub regions) and measurements of cerebral blood flow dynamics. These novel MRI scans will be analyzed to establish the role of two related stressors that impact the health of these AD vulnerable brain regions: 1) sleep quality, and 2) cerebral vascular flow pulsatility. The new analyses were not part of the aims of the ongoing NIH study. Sleep quality: Sleep quality significantly impacts brain health. Recent publications suggest that removal of toxins from the brain through the cerebral spinal fluid (CSF) circulation occurs primarily during sleep. Thus, impaired sleep may be a risk factor for accelerated cognitive decline and AD through inefficient maintenance of the brain tissue. In a small cohort of cognitively intact elderly subjects we found that subjects with poor sleep quality (not related to sleep apnea) had significantly smaller AD vulnerable regions (e.g., hippocampus [primarily left hemisphere], right inferior-parietal regions, left middle-temporal) compared to good sleepers. We proposed to perform a more refined brain parcelation of the middle temporal lobe and the hippocampus sub-regions to test for a link between sleep pattern of brain volume loss. We also will assess the surrounding CSF spaces as estimates of toxin clearance efficacy. Cerebral vascular pulsatility Dementia is associated with endothelial and blood-brain barrier dysfunction, i.e., the tight junctions between endothelial cells lining the vessels that prevents toxins and large molecules from entering the brain. We have found in a small cohort of patients with cognitive impairments that measures of vascular pulsatility are predicted the accelerated atrophy in the AD vulnerable brain regions. We hypothesize that aging related deterioration in the ability of the cerebral vasculature to moderate the blood flow pulsation (due to loss of cerebral vascular mechanical compliance) causes expansion of the cerebral microvascular during each cardiac cycle, which in turn, stresses the tight junctions and causes weakening of the tight junctions. The new funding will enable us to study a small cohort of younger healthy subjects to establish age related normative values of the cerebral vascular pulsatility measures as a normative reference. New knowledge that will emerge from our project will lead to the development of interventions to reduce the potential harming effects of these stressors.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
David Loewenstein, PhD	University of Miami	The Relationships between Multimodal Neuroimaging Biomarkers and A Novel Cognitive Stress Test (CST) Among Ethnically Diverse Older Adults	This application proposes a consortium between the University of Miami, University of Florida, Florida International University and Mount Sinai Medical Center and would generate an unprecedented opportunity to study state-of-the-art multi-modal neuroimaging (amyloid, tau, cortical thickness, regional brain volumes) and novel cognitive markers of early Alzheimer's disease among diverse ethnic and cultural groups (African-American, Hispanic and White-Non-Hispanics) at risk for Alzheimer's disease. This consortium will be the first in the State of Florida to examine the relationship between tau and amyloid load in the brain as they relate to novel cognitive stress tests that have been found to be extremely sensitive markers of PreClinical AD by uniquely tapping susceptibility to proactive semantic interference (PSI) and failure to recover from PSI (frPSI). The consortium will leverage existing resources and data provided by the 1Florida ADRC and the University of Miami's longitudinal NIH study on aging and cognition (Dr. Loewenstein, PI) and will recruit additional minority older adults at risk for AD. The proposed consortium will also leverage the complimentary expertise offered by Drs. David Loewenstein and Rosie Curiel (University of Miami), Dr. Steven DeKosky (University of Florida), Dr. Maria Grieg (Mount Sinai Medical Center) and Dr. Malek Adjouadi (Florida International University). Our laboratories provide special expertise in quantitative multimodal neuroimaging, diagnosis of early cognitive impairment (MCI and PreMCI states), and the development of novel cognitive stress paradigms that are cross-culturally sensitive. The goals of this consortium are to determine 1) whether ethnically diverse older individuals who exhibit PSI or frPSI deficits are at greater risk for AD related pathology (amyloid and tau load in AD prone areas) and 2) relate these predictors to more ubiquitously available imaging measures such as cortical thickness and brain volumes in AD prone regions (e.g., hippocampus, entorhinal cortex, precuneus, posterior cingulate). This consortium integrates unique expertise from three productive and outstanding institutions, focuses on state-of-the art-multimodal neuroimaging methods used to detect preclinical AD, leverages excellent diagnostic work-ups in African-American, Hispanic and White Non-Hispanic elderly as well as existing MRI, novel cognitive stress tests and amyloid data. Such a study is of high impact in that it expands upon and further refines diagnostic strategies for early detection of PreClinical AD and emerging treatments. It will also yield important pilot data for successful collaborative R01 and other federal grant submissions to the National Institutes of Health.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Michal Toborek, MD, PhD	University of Miami	Extracellular Vesicles as Novel Therapeutic Targets in Alzheimer's Disease	Virtually all cells of the human body shed vesicles into the extracellular space, which then travel via the blood stream and can reach distant organs. These vesicles, named "extracellular vesicles" (ECV), carry content characteristic to the cells they originate from, including a protein called amyloid beta (Abeta). We propose that ECV can bring Abeta from the periphery into the brain by crossing the blood-brain barrier (BBB), a critical interface built by the brain micro-vessels, which normally protects the brain from blood-borne factors. Moreover, we postulate that this process is accelerated in Alzheimer's disease (AD), and contributes to Abeta accumulation in the brains of individuals suffering from AD. Increased deposition of Abeta in the brain is of critical significance because it generates pathology that involves memory loss and cognitive decline in AD individuals. The link between elevated Abeta levels in the brain and loss of memory in AD is not fully understood. However, it is important to note that neural progenitor cells (NPC), i.e., cells that produce new neurons even in the adult brain, are located in close proximity to brain micro-vessels forming the BBB. NPC-derived neurons are critically important for normal brain function because they are built into normal neuronal networks and participate in memory formation. Our proposal will explore the role of ECV in Abeta transfer to NPC and the outcomes of this process, such as impaired production of new neurons, resulting in memory loss. The central hypothesis of the proposal is that Abeta carried by ECV across the BBB impairs formation of new neurons from NPC, resulting in memory loss. Specific mechanisms evaluated in this application include studies on the uptake of ECV and delivery of Abeta cargo to NPC (Aim 1), the impact of this process on the formation of new neurons from NPC (Aim 2), and alterations of cell communication between NPC (Aim 3). The studies proposed in this application are pre-clinical and involve cell cultures and animal experimentations. Overall, our proposal offers a unique perspective on the interactions between the BBB, ECV, and Abeta deposits on impaired formation of new neurons in adult brain. We expect that therapeutic targeting of this process can protect against Abeta pathology and memory loss in AD.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Anthony Griswold, PhD	University of Miami	Identification of Noncoding Functional Variant(s) Underlying Alzheimer Disease GWAS Hits	Alzheimer's disease (AD) is the leading cause of dementia in the elderly and its prevalence is on the rise. Recent genome wide association studies (GWAS) have identified at least 20 genetic markers associated with AD. Unlike known autosomal dominant pathogenic mutations in genes such as amyloid precursor protein, presenilin 1, and presenilin 2, the majority of associated GWAS variants (~77%) are located in non-protein coding regions of the genome. While it is hypothesized that these variants and/or variants in linkage disequilibrium (LD) with them alter regulatory elements thereby changing gene expression, identifying the functional variant contributing to risk in noncoding regions is complex. First, the index variant from GWAS may not be functional. Rather any of the variants in LD with the index could be the molecular 'driving' variant. Second, regulatory regions can lie significant distances away from the genes that they modulate. Thus, the nearest gene to the index variant may not be the gene whose expression is modified. Lastly, chromatin structure and epigenetic marks are often tissue specific. As such, there remains a gap in knowledge regarding the molecular mechanisms altered by the AD associated variants. Since characterization of 20 AD GWAS associated variants is outside the scope of this project, we will focus on variants in the PICALM genome locus. This locus has been replicated as a highly significant AD associated region, however, despite significant re-sequencing efforts, no coding or other functional variants have been identified. Therefore, this represents an excellent opportunity to identify functional regulatory variants alterations in this region, understand how they affect cellular biology, and establish a protocol to expand this to other GWAS loci. Through a systematic, multidisciplinary genomic approach we will characterize variants in the PICALM locus to identify the underlying biology the associations represent by accomplishing the following aims: 1) Develop a massive parallel reporter assay (MPRA) to identify effects of variation on gene expression. First, we will use publically available data on histone modifications and transcription factor binding sites in AD affected brain regions to prioritize regions of interest within the PICALM region. Then, we will directly query alternative haplotypes in those regions for effect on gene expression with an in vitro massively parallel reporter approach to identify the specific variant(s) in the region exerting regulatory capacity. 2) Determine biological effects of candidate functional variants. We will further characterize regulatory variants in a cellular model approach using induced pluripotent stem cell (iPSC) derived neuronal cells (e.g. cortical neurons and/or microglia) modified to reflect the identified variant by genome- editing technology (e.g. CRISPR/Cas9). AD-specific (e.g. production of amyloid beta) and general cellular phenotypes (e.g. cell viability and lipid transport) will be evaluated. This proposal will help develop a streamlined protocol to study large noncoding regions in the context of AD. The identification of functional noncoding variants in AD can lead to novel entryways in treatment of AD delaying onset or progression of disease. We aim to identify pathways involved early in neurodegeneration, increasing the impact of new treatment options through its potential application in multiple disorders.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Derek Dykxhoorn, PhD	University of Miami	Investigating the Role of SORL 1 in Alzheimer's Disease	Alzheimer's disease (AD) is the most common cause of dementia in the elderly. There are currently more than 5 million individuals in the United States diagnosed with AD and, as the average age of the population rises, so will the incidence of AD. While genetics has been shown to play an integral role in AD risk for over two decades, understanding the underpinning mechanisms which cause disease is still ongoing. We propose to focus this study on SORL1, a gene that has been implicated in both early and late onset AD. We have generated two stem cell lines from affected individuals who carry a single base pair deletion in SORL1 that produces a truncated protein, predicted to have potentially pathogenic consequences. We will compare these stem cells to those created from gender and aged match normal individuals. These stem cells can be differentiated into neurons, a disease relevant cell type, to recapitulate disease progression. These neurons will be evaluated as they age for morphological changes in shape and connectivity, as well as being tested for cellular changes in proteins related to AD including amyloid beta and tau. In addition to generating traditional 2D neuronal cell cultures, we will also create 3-dimensional organoids that more faithfully mimic the neurogenesis process. Organoids are comprised of both neurons and their supporting cells, glia and astrocytes, and will allow us to more clearly decipher cell specific roles of SORL1. We will then use genetic tools to introduce the single base pair SORL1 deletion into the control lines and, in a reciprocal experiment, revert the change back to normal in the AD cases. Both the original and edited versions of all of the stem cell lines will be grown under conditions that induce them to become neurons, a relevant cell type to study AD. Through these experiments, we aim to determine if the SORL1 change results in AD specific consequences in neuronal cells and if correcting this genetic change can fix the cellular abnormalities. We hope to reveal the role that SORL1 plays in AD pathology, as well as gain a greater insight into how SORL1 acts in a similar or distinct manner from other causes of AD. This will address the Priority Area 2 and delve into a deeper understanding of the mechanisms of neurodegeneration (Focus Area 2.2) as well as the biological basis of novel genetic risk factors in Alzheimer's Disease (Focus Area 2.5).

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Maj-Linda B. Selenica, PhD	University of South Florida	Emerging role of tau citrullination in Alzheimer's Disease	Alzheimer's disease is a progressive, devastating form of dementia that affects not only patients but also their caregivers, worsening the quality of life for everyone affected by the disease. Although a number of therapeutic strategies are in clinical trials, there is no cure for the disease. Tau pathology is one of the hallmarks of Alzheimer's disease and encompasses accumulation of aggregated tau in neuronal neurofibrillary tangles, followed by neuronal death and cognitive decline. Several post-translational modifications are identified to contribute to pathological tau, phosphorylation being the most major event in tau and widely studied. We have uncovered a novel posttranslational modification of tau, citrullination, caused by the enzyme peptidylarginine deiminase 4(PAD4). To this end, we will use a mouse model of tau pathology to test whether reduction of citrullinated tau rescues pathology. Thus, we propose to genetically down regulate expression of PAD4 in this model and the healthy controls to reduce tau citrullination. Following treatment, we will assess whether reduction in citrullinated tau also results in reduction of overall pathology; including tau phosphorylation, neurodegeneration, inflammation and improvement in behavior performance. A separate group of mice will be immunized with tau peptides that are chemically modified to include either a citrullinated or phosphorylated site. Under this paradigm we will analyze whether the immunization is able to reduce citrullination of tau, rescue pathology and improve cognition. In addition, because tau pathology plays a role in the inflammatory milieu of the Alzheimer's disease brain, we will examine levels of microglia activation in immunized mice compared to control mice. This work will provide a foundation for translational strategies to improve the lives of patients with Alzheimer's disease by reducing some of the most severe symptoms of the disease.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Kevin Nash, PhD	University of South Florida	Microglial Phenotype in Alzheimer's Disease	Chronic inflammation promotes the progression of neuron loss in Alzheimer's disease (AD) and other neurological disorders. It is our hypothesis that reducing the brain immune activation will slow the development of disease, however, our current understanding of the complex contribution of inflammation is very limited. Therefore, in Aim 1 we will examine the profile of the inflammatory cells of the brain, called microglia. This will characterize how the microglia are altered in AD and may offer up as yet unidentified ways we could decrease the inflammation. We do know that the protein fractalkine and its receptor are an important part of inflammation control in the brain. We have shown that increasing fractalkine can reduce pathology in both an Alzheimer's disease and Parkinson's disease models, however, we currently do not understand the mechanism of action of fractalkine on microglia. In Aim 2 we will examine how fractalkine alters inflammation to be beneficial rather than detrimental. To do this, we will use a gene therapy approach to deliver fractalkine into a mouse model of AD and then examine how the inflammation and the microglia are altered. Our long-term goal is to develop a therapeutic approach that will modulate the immune activation to one that minimizes the development of disease and subsequent neuron death. This proposal is a critical step in furthering our understanding of how inflammation is contributing to neuron loss and how we may alter it to prevent this loss, which will be immensely valuable to the research community in determining novel therapeutic targets that have yet to be explored for neuron loss

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David E. Kang, PhD	University of South Florida	Divergent RanBP9 signaling in tau pathogenesis	Alzheimer's disease (AD) is a devastating neurodegenerative disorder of the brain that afflicts more than 5.4 million people in the United States and close to 500,000 people in Florida. At present however, there are no effective treatment or therapy for AD. Two major pathologies – namely amyloid beta (Abeta) plaques and tau tangles – are responsible for the neurodegenerative changes seen in AD brains. Tau pathology is common to multiple neurodegenerative diseases, including Alzheimer's disease (AD), Frontotemporal dementia (FTD), Progressive Supranuclear Palsy (PSP), Corticobasal degeneration (CBD), and others. However, AD is unique in that Abeta accumulation is thought to be a principal driver of tau pathology. Despite the pivotal significance of Abeta in AD, multiple studies have also shown that Abeta-induced neurotoxic signals require tau, since the loss of tau abrogates many deleterious effects of Abeta. Thus, molecular intermediates of Abeta to tau signaling represent attractive molecular targets for therapeutic intervention. However, at present, a significant knowledge gap exists in terms of how Abeta pathogenically impinges on tau. Our findings indicate that the scaffolding protein RanBP9, which is highly elevated in brains of AD patients, functions as a molecular intermediate between Abeta to tau signaling and ultimately promotes tau pathology via 2 divergent pathways: 1) Hsp90/Hsc70-based preservation of tau; and 2) cofilin-induced dislodging of tau from microtubules. However, we do not know whether or how RanBP9 alters the aggregation of tau via its direct association with tau and/or Hsp90/Hsc70 complexes nor do we know precisely which activation state of cofilin promotes tau pathology in brain. In this proposal, we will seek to answer these important questions, which will further the understanding of Abeta-driven tau pathogenesis and aid in the development of potential therapeutics for AD. To answer these questions, 1) we utilize combinations of purified recombinant proteins (RanBP9, tau, Hsp90, & Hsc70) to determine how these protein interactions alter tau aggregation and microtubule assembly. We will also determine the role of RanBP9 complexes with Hsp90 and Hsc70 on tau oligomerization and aggregation in cultured cells; 2) we will directly test the hypothesis that activated cofilin but not inactive cofilin promotes tau pathology by expressing defined cofilin variants in brains of tau transgenic mice (tau pathology model) to assess tau pathology, microtubule integrity, and other neurodegenerative changes.

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Principal Investigator	Principal Investigator's Organization	Project Title	General Audience Abstract
Daniel C. Lee, PhD	University of South Florida	Exploiting GPRC6a Antagonists to Mitigate Tau Deposition	Tauopathies consist of age-associated neurodegenerative diseases and remain a central target of Alzheimer's disease (AD) for which no disease-modifying treatments exist. One strategy for targeting protein aggregates observed in tauopathies involves increasing degradation. One of the most well studied pathways that govern cellular proliferation versus protein degradation (autophagy) comprise of the mechanistic Target of Rapamycin kinase Complex 1 (mTORC1). The mTORC1 pathway controls cellular stress, energy metabolism, amino acid levels, and is a primary target of diabetes, cancer, aging and neurodegenerative diseases. Although many reports have revealed mechanisms associated with mTORC1 regulation recent pivotal discoveries identified new cellular sensors for the mTORC1 pathway in lower order species but have evolved in mammalian species. Many chronic diseases associate with mismanagement of metabolism directly implicating mTORC1 as a probable target. Our group has uncovered a unique interaction between arginine metabolism, arginine-sensing receptors and arginine-sensing proteins with tau biology. Arginine metabolism shows considerable influence upon tau biology. We show that arginase 1 (Arg1) reduces many aspects of the tau phenotype and posit that the depletion of arginine increases autophagy through amino acid-sensing. GPRC6a is a G-protein coupled receptor recently discovered and shown to bind with high affinity to Larginine. While it remains unclear as to the exact role of GPRC6a, we postulate that GPRC6a associates with mTORC1 signaling and autophagy. Our central hypothesis states that decreased signaling of GPRC6a reduces mTORC1 signaling, activates autophagy and increases tau clearance. We posit that GPRC6a remains tonically activate and senses extracellular amino acid abundance of L-arginine during neurodegenerative conditions. We will elucidate a mechanism by which GPRC6amodifies tau metabolism in vitro and in vivo using several approaches: genetic knockdown ofGPRC6a, a new class of GPRC6a antagonists, neuronal cellular models that measure tau metabolism and oligomerization, and mouse models of tauopathy. These are the first studies to potentially link this new deorphanized receptor (GPRC6a) to autophagy suffice through amino acid-sensing machinery using arginine signaling to clear protein aggregates. Our preliminary data, which show that our novel allosteric antagonists clears tau deposits, and remains consistent in numerous Alzheimer's disease (AD) like models. This proposal will allow us to provide "a function" relative to disease (AD and tauopathies) linked to this receptor. Success in this application would provide a new receptor target governing arginine sensing mTORC1 signaling, autophagy and predicted to mitigate the tau phenotype. We will also provide the first evidence for a new class of drugs aimed at extracellular arginine-sensing to combat tauopathies and AD.

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Andrew Keegan, MD	The Roskamp Institute	Longitudinal assessment of BDNF levels with Bacopa monnieri treatment in those at risk of developing Alzheimer's dementia	Alzheimer's disease (AD) is a neurodegenerative disease that progresses relentlessly, but it can have an insidious onset that early on is not always discernible from normal aging. Prior to overt, measurable memory deficits, individuals may display alterations in mood (e.g. depression, anxiety) or have subjective memory complaints. However, cognitive testing at this stage is often unremarkable (subjective cognitive decline). During this "preclinical" period and the critical years prior, there may be an opportunity to alter important circuitry in the brain in the regions of memory consolidation (hippocampus) and emotion (amygdala) thereby reducing risk of progression to Alzheimer's dementia. These brain regions have been shown to be atrophied in persons with AD as well as those with depression without dementia. More importantly, and possibly prior to this atrophy, certain factors important to maintaining synaptic connections such as brain-derived neurotrophic factor (BDNF) may be reduced. Some studies have shown that low BDNF may put someone at greater risk of developing AD, and one large longitudinal study revealed that elevated BDNF may be protective from developing AD. Therefore, one approach of disease prevention may be to improve BDNF levels prior to and during the preclinical years. It is well known that important lifestyle choices such as exercise will reduce risk of developing AD and interestingly exercise has been associated with increasing BDNF levels (although there are likely many factors surrounding exercise benefits). It has also been shown that major stressful events may result in lowering BDNF. Additionally, there is evidence that commonly used anti-depressants including selective serotonin reuptake inhibitors (SSRI's) can raise BDNF in the treatment of depression but also alter amyloid levels in the spinal fluid both of which may be important for slowing the onset of AD. With these encouraging findings, there are plans to evaluate SSRIs as treatment as a preventative for AD, but there are other substances that can influence BDNF levels as well as amyloid processing. Bacopa monnieri is an Ayurvedic herbal that has been used for centuries for a variety of purposes including cognitive enhancement. Animal studies support multiple mechanisms of Bacopa including those important to AD: reducing amyloid pathology, increasing free radical scavenging, improving vascular flow, and increasing BDNF. In addition, the clinical data illustrates a good safety profile of Bacopa with multiple small studies showing efficacy in enhancing cognition and treating mood disorders. Our primary objective is to assess the effect of Bacopa on BDNF levels and other blood based biomarkers over time in an at-risk population for AD. Secondary objectives will include assessments of cognition and mood as well as safety labs. We will account for exercise and stress during this treatment period and incorporate other factors such as APOE and BDNF genetic carrier status. As clinical interventions move to alternative strategies beyond primarily modifying amyloid and/or tau, the focus on preserving or improving synaptic plasticity will likely be included. The above study may offer insight into some of these mechanisms while we wait for newer agents in phase 3 clinical trials for depression (ketamine related agents: esketamine, rapastinel) that may also offer hope in treating dementia due to potential synaptogenesis.

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