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Principal Investigator	Principal Investigator Organization	Project Title	General Project Abstract
Rosa Rademakers	Mayo Clinic Florida	Identification of novel AD genes and disease associated pathways through FPADS: a Florida Presenile Alzheimer's Disease Subjects registry	This proposal aims to set up a registry of early-onset Alzheimer's disease (AD) patients across the state of Florida and to aid in the identification of novel AD genes and disease pathways. The identification of genes responsible for early-onset familial AD has been instrumental in defining the amyloid cascade hypothesis, a leading hypothesis in AD research to date, which underlines the importance of genetic discoveries in these early-onset cases. Genetic studies by us and others however made clear that additional early-onset AD genes await identification. Since the availability of systematically ascertained, large cohorts of AD patients is critical for such gene discoveries and for future clinical and translational studies, we propose to build FPADS, a registry to collect biospecimens of early-onset AD patients across Florida for use in clinical and genetic research (Aim 1). This patient cohort and the collaborative network of investigators at 5 major sites (Mayo Clinic Florida, University of Florida, USF Health Byrd Alzheimer's Institute, University of Miami and Mount Sinai Medical Center) are expected to foster collaborations across the State and drive future scientific discoveries aimed at a better understanding of AD pathogenesis. To maximize the impact of our proposed research within the allowed 5 month time-frame, we will also perform genetic and cell-based studies in parallel to the patient recruitment in FPADS. For these studies we can build on our existing cohorts of patients ascertained at Mayo Clinic and the Florida brain bank, as well as our preliminary studies which already highlighted several novel potential AD genes. Exome sequencing combined with high-density genotyping will be used to identify novel candidate AD genes in both familial and sporadic AD patients (Aim 2). The effects of mutations in potential novel AD genes will be further studied in cell culture and in human brain samples (Aim 3).

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David Loewenstein	University of Miami Miller School of Medicine	A Consortium to Study Novel Markers of 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 "Four Institute AD 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 building a" Four Institute AD Consortium" involving the University of Miami School of Medicine (UM), the University of Florida School of Medicine (UF), the Wien Center for Alzheimer's Disease at Mount Sinai Medical Center (MSMC) and the Center for Advanced Technology and Education and Florida International University (FIU) and combining expertise in novel, sensitive neuropsychological assessment in culturally diverse populations; functional assessment; genetics; as well as clinical-translational informatics. We intend to focus on the development of novel and sensitive cognitive, functional and imaging methods to identify the earliest stages of AD as well as to build a sophisticated computational multimodal neuroimaging platform, and develop a central repository of data collected from the clinical sites. This work will be critical in building an 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 AD.

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Nilufer Ertekin-Taner	Mayo Clinic	Florida Consortium for African-American Alzheimer's Disease Studies (FCA3DS)	Our proposal "Florida Consortium for African-American Alzheimer's Disease Studies (FCA3DS)" is in response to the Florida Health Ed and Ethel Moore Alzheimer's Disease Research Program and directly addresses one of the key research areas outlined in the Funding Opportunity Announcement (FOA). As also stated in the FOA, late-onset Alzheimer's Disease (LOAD) is a deadly and costly epidemic, which disproportionately affects African-Americans. Despite being at twice as great a risk for LOAD as Caucasians, African-Americans remain underrepresented in AD research. This is a major impediment for progress against AD for this population because, also as stated in the FOA, "different groups are vulnerable to different risk factors". Currently, no curative therapies exist for LOAD. Identification of genetic risk factors is crucial to identification of drugs for AD, also a key research area according to the National Alzheimer's Plan (NAPA). The success of genetic studies depends on the availability of sizable cohorts and concerted multi-institutional efforts, both of which are lacking for African-Americans. Our proposal aims to overcome this gap in research by establishing the consortium, FCA3DS, that will lay the groundwork for the infrastructure required to enhance AD research in Florida, in this understudied population. Our proposed consortium currently includes four Florida institutions; Mayo Clinic, University of Florida, Mount Sinai Medical Center and University of South Florida. Our specific aims are to: 1) Build the collaborative infrastructure for FCA3DS; 2) Collect blood samples for future studies (100 LOAD and 100 elderly control African-Americans); 3) Identify novel LOAD genetic risk variants by whole exome sequencing (WES) in 250 subjects. We recognize that this 5-month grant has a limited focus, though we fully expect to generate resources and data in this duration that will be useful beyond this initial scope. We expect that the infrastructure built with this grant will enable future studies.

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Jada Lewis	University of Florida	Developing biotherapies for Alzheimer's Disease	Alzheimer's Disease is characterized by the loss of neurons and the accumulation of two proteins in the brain - tau and amyloid beta. Despite the rapid growth of our aged population and thus the population at risk for Alzheimer's Disease, the therapeutic landscape for this disorder is bleak. Our proposal is aimed at changing the way the field approaches identifying potential therapies for Alzheimer's Disease. Namely, we stop focusing on the impact of any one drug and pursue a combinatorial approach. Additionally, we will broaden our definition of "drug" to include "biotherapeutics" which will be the focus of our current approach. We will use this approach in a mouse model co-developed by one of the PIs which develops tau pathology and neuronal loss similar to that observed in Alzheimer's Disease. Ultimately, our proposal should discover new biotherapeutic modifiers for the tau-associated neuronal loss observed in Alzheimer's Disease.

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Sylvain Dore	University of Florida	Therapeutic potential of PGE2 EP1 receptor selective antagonist.	Stroke and AD are neurodegenerative diseases that are costing conditions and likely worsen the prognosis of each other. Based on our preliminary studies obtained from one of the common mouse model of AD, we demonstrated that a very brief stroke caused much more severe neuronal damage in AD mice than in wildtype control mice. Furthermore, we generated a new transgenic mouse in which we deleted the pro-inflammatory PGE2 EP1 receptor and we discovered that this was sufficient to remarkably reduce amyloid production, hippocampal neuron loss and memory loss. NOW, we need to test if by using a drug – that has been used in the clinic – that blocks this receptor will also prevent neuronal loss and the associated memory deficit. Thus, the main goal is to test the efficacy of a selective antagonist (i.e., ONO-8713) to improve anatomical and neurocognitive outcomes following stroke in AD mouse models (i.e., APPswe/mPS1, APP23, Tg2576). The use of these complementary AD mouse models is justified because they have different AD anatomical and vascular pathologies at the 3.5mo when the stroke is being performed. Then, therapeutic administration of the drug should limit all stroke outcomes. We will performed extensive anatomical and behavioral (motor and cognitive) tests using state of the art unbiased analyses. In addition, brain levels of soluble and insoluble specific Aβs peptides will be measured. Depending on outcomes, we also plan to extend the testing in females. All resources, unique tools, and expertise are readily available to successfully test this hypothesis. We believe that small-molecule GPCR drugs, such as this EP1 receptor antagonist, can be tested in order to limit many hallmarks and symptoms associated with AD, notably following an acute insult. Together, this will provide the necessary preclinical data to more such drug to the clinic with the optimal trial design.

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Carlos T. Moraes	University of Miami, Miller School of Medicine	The Role of Mitochondrial Oxidative Phosphorylation Dysfunction in Alzheimer's Pathology	The cause of Alzheimer's Disease (AD) is unknown, but there is evidence that defects in energy production by mitochondria have a major role in the neuronal loss. We will explore this hypothesis by using genetically-modified mice produced and characterized in our lab. These mice have AD pathology and defects specific for different parts of the mitochondrial energy generating system.In addition, we will test whether improving mitochondrial function can ameliorate the neurodegenerative features of AD, by subjecting the AD mouse model to three innovative approaches targeting the mitochondrial energy production system. These experiments will provide new leads for therapeutic interventions in AD.
David Kang	University of South Florida Health	Targeting the Slingshot-Cofilin Pathway in AD	Alzheimer's disease (AD) is a devastating neurodegenerative disorder of the brain that afflicts more than 5.4 million people in the United States and close to 500,000 people in Florida. At present however, there are no effective treatments or therapeutic 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. Our studies have found that the Slingshot-Cofilin pathway not only promotes amyloid production but also links amyloid with tau pathologies. In this project, we will use computational and biochemical techniques to screen for and identify drug-like inhibitors of Slingshot protein and use a gene therapy approach to determine whether Slingshot and Cofilin variants (with enhanced or inhibitory function) can ameliorate or exacerbate AD pathology in an animal model of AD. The results of these studies 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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Guojun Bu	Mayo Clinic Florida	ApoE and gender effects on Alzheimer's disease and cerebral amyloid angiopathy	Alzheimer's disease (AD) is the most common form of dementia caused by accumulation of toxic amyloid-β (Aβ) peptides in the brain. While Aβ often deposits on brain vessels as cerebral amyloid angiopathy (CAA) which damages vessel walls and causes bleeding in the brain among aged individuals, such brain vascular damages also in turn disturb Aβ clearance and thus further increase the risk for AD and CAA. Genetically, the APOE4 gene is the strongest risk factor for AD and CAA among the three polymorphic alleles. APOE gene encodes apolipoprotein E (apoE) whose main function is to transport cholesterol. ApoE also regulates Aβ clearance and brain vessel functions, where apoE4 is inferior compared with other isoforms. Epidemiological studies have shown that women are more likely to develop AD than men. Interestingly, APOE4 effect is significantly stronger in women compared to men. On the other hand, brain vessel damages such as stroke are more frequent in men than women. We also found that men have more severe CAA than women in AD. Thus, we hypothesize that apoE isoforms and genders contribute to AD and CAA pathogenesis by differently influencing brain vessel functions and Aβ clearance. In this proposal, we plan to use pathological and biochemical tools to address our hypothesis by analyzing a large autopsy brain collection from AD patients at Mayo Clinic. We also aim to discover novel genes and functional networks in AD and CAA pathogenesis by comparing AD brains with or without CAA through system-based, multidisciplinary approaches including RNA-sequencing, metabolomics, lipidomics and whole-exome sequencing. These studies should generate clues as to how these diseases are influenced by gender-specific and apoE-related pathways. If successful, our proposed project should allow us to understand mechanisms and discover new pathways and therapeutic targets for brain vasculature-related diseases including AD and CAA.

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Claes Wahlestedt	University of Miami Miller School of Medicine	Epigenetic approach for the treatment of Alzheimer's disease	Alzheimer's disease (AD) is the most common form of dementia in the elderly. It has become increasingly clear that therapies involving a single drug target may not be sufficient in treating AD. Considering the large amount of genes that have been linked to AD, means of addressing all of them turn out to be extremely difficult. Experts in the AD field are realizing that a solution will have to be the use of "drug cocktails"; but such a tactic presents challenges in terms of clinical and regulatory hurdles. We therefore took an epigenetic approach where a single drug would simultaneously affect the expression of a number of defined AD-related targets. Epigenetic drugs allow one to increase or decrease the levels of target genes without affecting the DNA sequence. Many of these types of drugs are considered safe and are currently undergoing clinical trials for different cancers. After screening our in-house comprehensive library of epigenetic drugs, we identified a small molecule, CTI-309, that reduces a number of key players in AD progression such as beta amyloid (Aβ) protein, as well as BACE1 and tau gene expression; while increasing the expression of a number of neuro-protective genes: BDNF, α-secretase (ADAM10), Mint2, Fe65 and REST. The molecule CTI-309 is particularly interesting because it has a good safety profile and it affects AD-related genes in the brain of animals. We propose to elucidate the mechanism of action of CTI-309 using gene silencing experiments. We plan to synthesize new small molecules that are even better than CTI-309, which would allow the use of lower doses of the drug for treatment. Finally, we plan to test CTI-309 and the best newly synthesized drug in AD animal models to see if we can prevent learning and memory impairment.

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Jun Tan	University of South Florida	Flavonoid-diosmin, a novel gamma-secretase modulator, for the treatment of Alzheimer's disease	Key in the pathogenesis of AD is the deposition in the brain of two proteins, β-amyloid (Aβ) and tau, in the form of plaques and tangles. β-amyloid is produced by the cleavage of a protein called Amyloid Precursor Protein (APP) by the enzyme γ-secretase. Since γ-secretase is important in the production of Aβ and plaques, as well as the subsequent development of tangles and inflammation in the brain, γ-secretase has been targeted for years in the development of AD therapies. However, recently it has been shown that γ-secretase activity plays an important role in the ability of microglia, the resident immune cells, to remove Aβ plaques from the brain. Thus we sought to develop a new class of γ-secretase modulators (GSMs) which can reduce APP cleavage while minimizing their effect on microglia. We have recently found that the citrus flavonoid, diosmin, reduces Aβ formation, plaque and tangle deposition, and inflammation, while enhancing the removal of Aβ by microglia, in both cellular and mouse models of AD. This therapeutic effect of diosmin was further shown to be mediated by inhibition of the enzyme GSK3β. Here, we will fully characterize the ability of oral administration of diosmin to reduce AD pathology (plaques, tangles), while preserving the ability of microglia to remove Aβ plaques, in the brains of 3XTg-AD mice, a more appropriate model of human AD. We will test the ability of diosmin to elicit these effects when administered both before (prevention) and after development of AD pathology (therapeutic treatment). These studies will fully complement our recently NIH/NACCM-funded proposal which will investigate the ability of diosmin prevention and therapeutic treatment in reducing memory impairment in these mice. It is expected that the present proposal will lay the foundation for AD clinical trials with diosmin diet supplementation in the near future.

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Daniel C. Lee	University of South Florida	Modulation of Arginine Metabolism and Polyamines to Mitigate Alzheimer's disease Pathology	Currently no accurate measure for the number of neurodegenerative diseases exact but estimates suggest greater than 600 brain disorders exist impacting 100 million Americans and costing more than $5billion according to NIH. More than 15 different tauopathies including Alzheimer's disease (AD) exist with increasing behavioral phenotypes presenting in the clinic. Tau correlates most closely to neurodegeneration when assessing various aspects of the AD pathology. Arginine metabolism remains a critical division point during cell biology and can dictate several outcomes. Arginine decarboxylase is an enzyme that metabolizes the amino acid L-arginine to make a molecule known as agmatine and subsequent polyamines. Polyamines (putrescine, spermidine, and spermine) remain highly regulated yet can become dysfunctional during disease. Agmatine has been identified in the brain and exerts a number of beneficial affects on other neuronal disorders shown to promote neuroprotection in stroke, epilepsy, Parkinson's disease models, and traumatic brain injury. It has also been shown to exert anti-depressant and anti-anxiety affects among others. However very little research has been done on agmatine in Alzheimer's disease, animal models, and related pathologies. We find that increasing other arginine metabolizing enzymes such as arginase 1 reduces tau pathology and various aspects of the tau phenotype in mouse models of tauopathy. This proposal will identify how arginine decarboxylase impacts tau pathology in an animal model of deposit tau. We will identify if increases in agmatine and subsequent polyamines impact tau pathology and cognition by overexpressing polyamine producing enzymes arginine decarboxylase or administering agmatine pharmacologically to mice. Studies proposed here will help identify the role of arginine metabolism, agmatine, and polyamine production during tau deposition.