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Alberta Alzheimer's Research Program (AARP) Round VII
Deadline: November 2018

Funded Proposals

Project Title	The ApoE/ApoER2 axis in cerebrovascular dysfunction in Alzheimer disease
Project Leader	**Dr. Minh Dang Nguyen**, University of Calgary
Funded	$150,000

Lay Summary
Alzheimer's disease (AD) is a debilitating brain disorder and the most common form of dementia in the elderly. Cerebrovascular dysfunction that includes the deterioration of brain microvessels and reduced cerebral blood flow, constitutes a common pathological feature in AD. The strongest genetic factor for AD encodes for a protein that transports lipids called ApolipoproteinE (ApoE). In humans, there are 3 subtypes of ApoE (E2, E3 and E4), and each of us carries 1 or 2 of these subtypes. Individuals carrying the ApoE4 allele have up to 15 times increased risk of developing AD.
ApoE protein is produced in the brain where it regulates neuronal functions. However, the majority of bodily ApoE comes from the liver, circulates through the blood to reach brain microvessels and interacts with specialized receptors on these vessels. Yet, how ApoE and particularly the ApoE4 subtype regulates brain vascular tone and cerebral blood flow remains totally unknown.
In this grant application, we propose to investigate the pathological roles of ApoE4 in cerebrovascular functions. Our work will shed new light onto the pathogenic mechanisms of this key predisposition factor in AD. We hope that knowing more about the biology of ApoE in brain microvessels will help us finding treatments to fix the impaired brain vasculature and memory impairment of AD patients.

Project Title	Unraveling the mechanism of action of PET-tracer interaction with fibrils in Alzheimer's disease for new and improved diagnostics
Project Leader	**Dr. Andriy Kovalenko**, University of Alberta
Funded	$150,000

Lay Summary
The relatively high rate of failures in developing therapies to treat Alzheimer's disease (AD), warrants the development of better diagnostic tools for early AD or pre-AD detection. An emerging approach for early AD detection is non-invasive positron emission tomography (PET) of the sticky protein aggregates in brain cells that seem to cause AD. However, the positron PET tracers developed over last decade to reach in to the affected neurons and bind to the sticky protein mass are plagued with problems such as low selectivity, rapid metabolic degradation, and poor organ selectivity. This has handicapped efforts to develop PET tracers for use in diagnosing and monitoring AD. A rapid developmental platform is needed to fast-track the screening, assessment and development of new PET compounds toward this goal. The main goal of this project is to use state-of-the-art molecular solvation theory in conjunction with experimental studies to understand the comparative binding modes and/or efficiencies of different "cold" (non-radioactive) forms of PET tracers that bind to the sticky proteins found in AD. This information will then be used to build (and later synthesize) a model of an ideal PET tracer structure needed for the high selectivity and good distribution properties need for early AD detection by PET. The complementary feedback between the experimental and the theoretical endeavors will be used enhance and expedite the process of developing new PET diagnostic agents for AD.

Project Title	Traffic Noise, the Aging Brain and Alzheimer's Disease
Project Leader	**Dr. Majid Mohajerani**, University of Lethbridge
Funded	$120,000

Lay Summary

Prevention of cognitive decline and delay of onset of Alzheimer's disease (AD) are public health priorities and improving brain health is a firm commitment of the Alberta Dementia Strategy and Action Plan. Since traffic noise exposures are pervasive and modifiable, they are an appropriate target for research on brain health. Evidence for traffic noise links to neurodegeneration is accumulating with recent studies implicating traffic-related air and noise pollution in lower cognitive function, cognitive decline, the incidence of AD and all-cause dementia, and brain atrophy. The effects of chronic traffic noise on neuropathology in the aging brain are unknown. Stress in adulthood has been associated with cognitive, social, and physical symptoms including deficits in emotional regulation, and motor and executive function. Studies with lab rodents have shown that perinatal stress produces many behavioral abnormalities and an elevated prolonged stress response. Gestational stress increases anxiety and alters neuronal morphology in adult offspring. Preliminary studies have shown that exposure to auditory noise, results in chronic increases in anxiety-like behavior, cognitive deficits, and reduced size of the specific brain regions. Using a transgenic mouse model of AD, our preliminary data suggest that noise stress in young adulthood or prenatally hastens the onset of AD-related symptoms. The goal of this project is to explore the effect of traffic noise on the acceleration of the AD symptoms, general cerebral plasticity, and cognitive functions. A deeper understanding of these environmental exposures will contribute to improvements in public health, particularly because these exposures can be modified by changes in regulations and individual behaviors.

Project Title	Dissecting the role of protein misfolding in SINE RNA-mediated hyper-activation of immediate early genes in Alzheimer's disease.
Project Leader	**Dr. Athanasios Zovoilis**, University of Lethbridge
Funded	$200,000

Lay Summary

Alzheimer's disease (AD) is one of the most common forms of protein conformational diseases that are associated with improper folding (misfolding) of proteins, which renders them toxic to the neural cells and causes death of brain cells and intellectual decline. Over 44 million people worldwide, among whom more than 6 million in the US and Canada, currently suffer from Alzheimer's disease or related dementia. Although some drugs may temporarily improve the disease's symptoms, no cure currently exists. This is partially due to the fact that the molecular cascade that leads from the misfolding of proteins to the observed AD symptoms is still unclear. This research aims to elucidate how protein misfolding triggers at the molecular level the events that lead to dysfunction and loss of brain cells. We focus on the interaction between protein misfolding and a class of RNA molecules called SINE RNAs, a class of non-coding RNAs that are not used for protein synthesis. In a recent publication (Zovoilis et al., Cell 2016) we showed that in mouse, the SINE B2 RNAs play a critical role in cell function by controlling expression levels of genes critical for the response to cellular stress and other studies point to a similar function for the respective human SINE RNAs called Alu RNAs. Recent advances in genomic sequencing technology enabled us to understand better the role of B2 RNA in protein misfolding and in a current Alberta Prion Research Institute funded project we have revealed the connection of B2 RNA destabilization with protein misfolding in an Alzheimer's disease mouse model. Supported by our interdisciplinary background in genomics and

neurosciences and a collaboration with the Calgary Brain Biobank, we try to dissect the molecular mechanisms underlying this process, understand the role of protein misfolding and SINE RNAs in the etiology of AD in humans, and contribute to the prevention and treatment of this debilitating and cruel disease.

Proposal Number	PAZ19011
Project Title	Functional significance of soluble oligomers, insoluble amyloid beta plaques and neurofibrillary tangles dynamics and deposition in the AD brain
Project Leader	**Dr. Majid Mohajerani**, University of Lethbridge
Funded	$149,000

Lay Summary

Alzheimer's disease (AD) is a disorder that results in degeneration of the brain which leads to severe memory impairments. This is a devastating disease producing personal and societal costs that are immeasurable and growing as the "baby boomers" age. Despite an intense global effort to understand the causes of AD it has been beyond the scientific communities grasp. One thing that is clear about AD is that the cause/s of the disorder is very complex and this idea is just starting to be appreciated. We embrace this complexity and will focus on a fascinating set of findings in the field that has established that some neurons become highly active in the early stages of AD when patients exhibit normal learning and memory. In the later stages of AD, neurons become less active with an accompanying decline in patients' mental abilities. The decrease in the activity of neurons is attributed to the presence of plaques around them and tangles inside them. Both plaques and tangles are fragments of proteins that get misfolded in AD. It is unknown where in the brain plaques and tangles emerge and how they contribute to changing the properties of neuronal circuits in the brain and leading to the progression of cognitive impairments. It is important to understand these early brain changes as they provide a target for therapeutic interventions early in the progression of the disease before significant and irreversible brain damage occurs. The proposed experiments aim to investigate the above mentioned questions in addition to finding in particular which neural circuits are responsible for spatial navigation deficits in AD patients which constitute as one of the earliest indicated symptoms.