NARFE Grants Awarded 8/31/2017 $466,450

1. Xinglong Wang $150,000 over 3 years
   Case Western Reserve University
   School of Medicine
   Cleveland, Ohio

Pathomechanisms of TDP-43 in Alzheimer's Disease – ***Does abnormal accumulation of the protein TDP-43 contribute to nerve cell loss in Alzheimer's Disease***

TDP-43 is a protein found in the brain. It is a hallmark of ALS (Lou Gehrig's disease) and also of frontotemporal dementia. Half of the people with AD also have clumps of this protein in addition to the plaques and tangles we are familiar with. We don't yet understand how this protein causes changes in the brain, but the initial studies indicate that TDP-43 may build up in small cellular structures that are needed to produce energy for cells. That unusual buildup could impair energy production and contribute to nerve cell loss in the brain.

Dr. Wang and his associates have planned a series of experiments to better understand what is happening. They plan to use nerve cells that have been grown in laboratory dishes to examine what factors may trigger the accumulation of TDP-43. The factors could include beta-amyloid, tau, or inflammation. The plans are to treat mice that have been given Alzheimer's symptoms with an inhibitor of TDP-43.

> **IMPACT**: Results of this study could shed light on the abnormal accumulation of this protein in the Alzheimer's brain. These findings could provide the first steps in testing a novel molecule that specifically inhibits TDP-43 buildup as a potential therapy to prevent nerve cell loss in patients with neurodegenerative diseases.

2. Hyun-Sik Yang $139,059 over 2 years
   Brigham and Women's Hospital
   Boston, Massachusetts

Pathophysiologic Link between TDP-43 Pathology and Alzheimer's Disease – ***Does abnormal buildup of the TDP-43 protein in the brain impact the progression of AD?***

The second researcher in the area of this TDP-43 protein is interested in investigating the link between the protein and the progression of AD. The accumulation of the protein is thought to be associated with brain shrinkage and cognitive decline, but how this actually happens is not yet known. They will study how TDP-43 affects brain structure in senior people with AD and without AD. They will utilize previous studies to base their own studies. (Religious Orders Study, Rush Memory and Aging Project, and Harvard Aging Brain Study) They want to determine if the protein accelerates the buildup of plaques and tangles to promote cognitive decline in people with AD.

> **IMPACT**: This study could shed light on how TDP-43 accumulation can affect the progress of AD and other dementias. It could also determine whether the specific protein could be targeted to develop new diagnostic and therapeutic strategies for such diseases.

3. Emily Edmonds, Ph. D. $149,995 over 3 years
   University of California
   San Diego, California

Longitudinal Cognitive and Biomarker Trajectories of MCI Subtypes – ***Can improved diagnosis of different types of mild cognitive impairment help predict who is at risk for AD?***

Dr. Edmonds is looking into the possibility of predicting who is at risk for AD and improved diagnoses. We know that the brain changes associated with AD begin many years prior the clinical symptoms. Mild Cognitive Impairment (MCI) is the transitional state between normal aging and dementia. People with MCI may have some changes in their memory functions, but no real problem with everyday activities. MCI includes people who have different types and different levels of impairment. The research is needed to determine how varieties of MCI may relate to the actual development of AD.

She and her associates will examine data from individuals of various subtypes of MCI. Some people may have difficulty only with memory, and others may experience trouble in language, still others may find problem solving a challenge. The researchers will review data collected over as much as ten years to determine who went on to develop AD and who remained cognitively stable. They plan to study (1) memory and thinking abilities, (2) the size of different brain regions using brain scans, and (3) the ability to complete everyday activities.

> **IMPACT**: We could learn novel information on long-term brain changes associated with different types of MCI. The work could also improve our ability to diagnose different types of MCI more precisely and better predict who may be at risk to develop AD.

4. Jole Fiorito, Ph. D. $27,396 (Partial)
   Columbia University Medical Center
   New York, New York

Drug development of novel PDE5 inhibitor for AD – ***Can a novel compound help preserve nerve cell function and prevent memory loss in AD?***

The final award was a partial grant to Dr. Fiorito, who is hoping to preserve nerve cell function and prevent memory loss in AD. Nerve cells "talk to each other" through synapses. The talk is necessary to support memory and other cognitive functions. In people with AD, the synapses become damaged. Recent studies indicate that inhibiting a molecule called PDE5 can help prevent synaptic damage and restore memory function. It has worked in Alzheimer's-like mice. Drugs are currently available to treat certain conditions in humans, but they are not optimized for the long term treatment of such diseases as AD.

Dr. Fiorito recently discovered a PDE51 that can effectively cross from the blood into the brain and reduce synapse damage. However, when tested in human liver cells, the drug is broken down too quickly indicating it may not stay in the body long enough to have effects. In the current studies, modifications will be developed to optimize the structure of the PDE51 to enable the PDE51 to enter the brain and ensure it selectively targets pathways involved in nerve cell synaptic function. They will test their novel product in Alzheimer's-like mice to evaluate its safety when given over long periods of time, and determine if it can help preserve synapses and improve memory function.

> **IMPACT**: These studies are the first steps in discovery and development of a drug that may prevent or reduce brain changes associated with AD. If successful, this effort could lay the foundation for future human clinical trials to determine if PDE51s are a therapeutic avenue for slowing or stopping the progression of AD.