Alzheimer's and Related Diseases Research Award Fund

FINAL PROJECT REPORTS FROM THE 2006-2007 ALZHEIMER'S RESEARCH AWARD FUND

The Alzheimer's and Related Diseases Research Award Fund (ARDRAF) was established by the Virginia General Assembly in 1982 to stimulate innovative investigations into Alzheimer's disease (AD) and related disorders along a variety of avenues, such as the causes, epidemiology, diagnosis, and treatment of the disorder; public policy and the financing of care; and the social and psychological impacts of the disease upon the individual, family, and community.

VCU Dusan Bratko, Dr. Sci. (Department of Chemistry) "Computer Screening of Amyloidogenic Protein Variants"

Ability to control or reverse protein aggregation is vital to the prevention or treatment of several neuropathological disorders including Alzheimer's, Parkinson's and amyotrophic lateral sclerosis. The impact of these diseases continues to motivate extensive investigations into the physics and chemistry of protein aggregation in search of key properties that can be modulated to suppress the process. These properties include environmental changes and sequence mutations that can often affect the ability of protein to aggregate. Systematic laboratory studies of a large number of protein variants and system conditions, however, are expensive and time consuming. Developing techniques for computer-assisted screening of potential mutations and varied solution conditions can significantly reduce necessary experimental efforts; moreover, molecular modeling provides essential microscopic insights that are not available through experiment alone. In the present research the investigator focused on the development of a novel computer simulation technique that combines the speed-up of multi-canonical computer sampling with the ability to simultaneously study a number of protein variants with similar sequences. The results confirm the feasibility of this new approach that will be developed further to enable a more efficient screening of polypeptide variants such as the mutants of the amyloid-β peptide, closely associated with Alzheimer's disease. Molecular insights emerging from computer models are also instrumental in unveiling general physical principles of peptide assembly important for successful control of disease-related protein aggregation processes. ***(Dr. Bratko can be reached at 804/828-1865)***

ODU Sheri R. Colberg, Ph.D., FACSM and colleagues (Department of Exercise Science) "The Relationship among Alzheimer's Disease, Dementia, Diabetes, and Physical Activity Status"

Diabetes increases an individual's risk of developing Alzheimer's disease and other forms of dementia or mild cognitive impairment, while regular physical activity has been shown to lower this risk. Thus, the purpose of this study was to examine the relationship among cognitive status, exercise status, and type 2 diabetes. The investigators studied a total of 145 subjects, 71 controls and 74 with type 2 diabetes, using a battery of tests that included two mental function scales, a depression scale, validated physical activity and self-care questionnaires, and various metabolic tests (e.g. fasting insulin, glucose, and cholesterol levels). The results demonstrated that diabetes has a negative impact on one of the cognitive measures employed. Moreover, cognitive scores were related to a number of metabolic parameters related to diabetes (i.e., blood glucose, fasting insulin levels, insulin resistance, and overall diabetes control). Scores were significantly associated with specific physical activity measures including hours spent doing light exercise during the week (like office work, driving, standing, and other daily activities), weekend sitting, and the number of days of exercise per week. Active individuals without diabetes were the least depressed group, and depression scores were associated with a number of physical activity variables. Certain types of physical activity appear to be beneficial for mental function and depression, particularly in people with diabetes, especially when it is less well controlled. These findings have implications related to the risk of developing AD or dementia due to diabetes and the risk reduction conferred by regular physical activity.***(Dr. Colberg can be reached at 757/ 683-3356 or 4995)***

VCU **Jeffrey L. Dupree, Ph.D. (Department of Anatomy and Neurobiology) "Understanding the Role of Sulfatide in Maintaining Viable Neurons in Alzheimer's Disease"**

Since neuronal death is the most prevalent pathology in Alzheimer's disease (AD), most research has focused on understanding intra-neuronal processes that regulate survival. The investigator proposes that other cells in the central nervous system (CNS) also play important roles in neuronal viability by creating an environment that facilitates survival. This hypothesis is supported by the finding that a prominent brain lipid, sulfatide, is significantly reduced in the earliest stages of AD. Sulfatide is an abundant CNS lipid that is almost exclusively produced by non-neuronal cells known as oligodendrocytes. Although best recognized for their role in myelin synthesis, oligodendrocytes also provide trophic support for neurons during development and assist in the establishment and maintenance of specific neuronal membrane domains. In addition, sulfatide is a sphingolipid, a class of lipids that is prominent in lipid rafts. In mice that are unable to produce sulfatide, oligodendrocyte-neuronal interactions are disrupted and axolemmal domains are compromised. The investigator's results strongly supported the hypothesis that a significant reduction of sulfatide in AD would result in abnormal raft composition, which in turn would facilitate altered enzyme activity and subsequently induce neuronal pathologic consequences. Using a sulfatide null mouse, the investigator found evidence that hyperphosphorylation of tau is induced in a subset of CNS neurons and that the abnormal phosphorylation is mediated by the kinase cdk5. Furthermore, he showed that this abnormal activity of cdk5 does not result from increased expression but rather from abnormal compartmentalization. Additional evidence showed that neuronal lipid rafts are disrupted in neuronal populations. These are the first findings to implicate a potential mechanistic consequence of sulfatide depletion in AD. Furthermore, it is likely that this pathologic mechanism may be initiated through oligodendrocytes.

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UVA **Ian G. Macara, Ph.D. and Huaye Zhang, Ph.D. (Center for Cell Signaling, School of Medicine) "The Role of Septins in Alzheimer's Disease"**

One of the pathological hallmarks of Alzheimer's disease (AD) is the formation of twisted neurofibrillary tangles inside the brain's nerve cells, which contain hyperphosphorylated tau proteins. Tau is a normal protein that is important for the function of nerve cells, but it is altered in AD so that it aggregates, and is believed to disrupt nerve cell function. In addition to tau, a family of guanosine triphosphate (GTP)-binding proteins known as septins is found in these tangles. The goal of this study was to determine the role of septins in tangle formation. The investigators have now found that one of the septin family members, Sept5, associates with tau in nerve cells. They also showed that Sept5 clusters together with tau in non-nerve cells. In addition, when excess Sept5 is present in the neurons, tau becomes misplaced, and clusters in the cell body with Sept5. This abnormal distribution of tau is reminiscent of that observed in AD patients. The next step was to examine how Sept5 alters the tau protein. Contrary to their original hypothesis, however, they could not identify a direct link between Sept5 and tau. Interestingly, however, they observed a consistent increase in the amount of tau protein in cells that over-express Sept5. This suggested that Sept5 somehow regulates tau protein levels. High levels of tau might aggregate and form tangles within neurons. Further investigation showed that the amount of tau in cells is regulated by how fast it is broken down (rather than how fast it is made). These results led to the hypothesis that tau breakdown, through a process that engages the ubiqutin-proteasome system, might involve a protein, called Parkin, which is known to bind to Sept5. Interestingly, Parkin is one of the genes responsible for Parkinson's disease. Ongoing experiments are aimed at examining whether Parkin is indeed involved in this process. If this is the case, these results could provide an unexpected link between AD and Parkinson's disease.

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GMU **Jeanne Sorrell, Ph.D., R.N. (College of Nursing and Health Science) and Catherine J. Tompkins, Ph.D. (Department of Social Work) "Ethics of Respect for Spirituality in Persons Living with Alzheimer's Disease"**

This interdisciplinary study sought to answer the question: How do members of a faith community describe experiences of spiritual connections related to Alzheimer's disease? The co-investigators implemented a grounded theory methodology to explore concepts that comprise spiritual pathways and to identify categories of spiritual connections within the social context of persons with Alzheimer's and their families living in a faith community. Two focus groups were held with clergy and 15 unstructured interviews were conducted with persons with early Alzheimer's or family caregivers. Participants reflected five different faith communities in Northern Virginia and the Shenandoah Valley. In-depth descriptions of participants' experiences were obtained in three primary focus areas: 1) Spiritual beliefs related to coping with Alzheimer's for both persons with Alzheimer's and caregivers, both in early and late stages of the disease; 2) Ways in which spirituality contributes to the overall concept of quality of life within a faith community; and 3) Ways in which members of faith communities facilitate or hinder the development of spiritual connections for persons with Alzheimer's and their families. Interviews were audio taped and transcribed verbatim. N-Vivo software was used to analyze qualitative data to identify conceptual themes related to spiritual dimensions of participants' experiences. Four conceptual themes were found related to living with Alzheimer's within a faith community: *Invisibility of Persons with Alzheimer's; Family Caregiver Stress and Isolation; Connecting through Spiritual Rituals;* and *Lack of Formal Preparation for Forging Spiritual Connections.* Findings from the study suggest a need for more formal preparation of clergy to understand how to forge and maintain spiritual connections with persons living with Alzheimer's; identification of social support systems within the faith community to address problems of stigma, isolation, and caregiver stress; and an organizational emphasis on integration of spiritual rituals such as communion, hymns, and prayers into the spiritual life of persons with Alzheimer's.

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