

Alzheimer's and Related Diseases Research Award Fund

2008-2009 ALZHEIMER'S RESEARCH AWARD FUND RECIPIENTS ANNOUNCED

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 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. The ARDRAF competition is administered by the Virginia Center on Aging at Virginia Commonwealth University. The five grant awards for 2008-2009 are:

Virginia Tech Paul R. Carlier, Ph.D. (Department of Chemistry) "Hydroxyethylamine isostere triazole-linked BACE1 inhibitors for Alzheimer's disease"

A vast array of evidence supports the hypothesis that Alzheimer's disease (AD) is caused by the build up of beta amyloid ($A\beta$) protein deposits, or plaques, in the brain. Although the approved therapies address the memory-loss associated with AD, none treat the cause. This project aims to develop new therapeutics that will prevent the formation of plaques in the brain and thus slow or arrest clinical progression of the disease. $A\beta$ is formed by the action of β secretase (BACE1 or Beta-site amyloid cleaving enzyme 1) on amyloid precursor protein (APP). The investigator aims to identify new potent and effective BACE1 inhibitors, using the enzyme to assemble its own inhibitor from a collection of building blocks. This innovative project features the use of *in situ* click chemistry and testing of the inhibitors in cell-based assays.

(Dr. Carlier may be contacted at 540/231-9219)

UVA Manoj K. Patel Ph.D. (Dept. of Anesthesiology) "Cleavage of sodium channel β 3 subunit by BACE1 and γ -secretase modulates sodium channel activity in neurons"

It has been proposed that the main substrate for BACE1 may not be APP, but rather the sodium channel auxiliary subunits, β 1, β 2, β 3 and β 4. Sodium channel β subunits play an important role in controlling sodium channel expression levels and activity *in vivo*. Studies have shown that in a similar manner to the APP protein, β subunits can also be cleaved to produce a free external portion and an internal portion. Cleavage of the internal portion of β 4 by BACE1 has recently been shown to control the expression of sodium channels on the cell surface. β 3 is also cleaved by γ -secretase, but the consequence of this cleavage on neuronal activity is unknown. Since sodium channels are critical for controlling the activity of neurons, and β subunits are important for fine-tuning this activity, these actions by BACE1 and γ -secretase could be an important mechanism for the progressive dementia associated with AD. In this project, the investigator seeks to correlate changes in hippocampal membrane excitability parameters (action potentials) with the actions of both the cleaved extracellular domain and the intracellular domain of β 3 on sodium channel activity and expression levels. *(Dr. Patel may be contacted at 434/924-9693)*

Virginia Tech Karen A. Roberto, Ph.D., Rosemary Blieszner, Ph.D., and Jyoti Savla, Ph.D. (Center for Gerontology) "Caring for a spouse with Mild Cognitive Impairment: Daily challenges, marital relations, and physiological indicators"

Although by clinical definition Mild Cognitive Impairment (MCI) is associated with minimal interference in activity of daily living and personal relationships, preliminary studies suggest a notable impact. This project will assess the daily frequency and intensity of the behavioral symptoms and challenges of those diagnosed with MCI, examining associations with spouse care providers' psychological and physical health and well-being. Thirty spousal partners will provide physiologic measures of stress symptoms and participate in daily telephone interviews, reporting the stresses and strains they experience. Within- and between-person variability will be examined to further understanding of the day-to-day challenges facing families dealing with early memory loss. The results will provide a framework for subsequent studies to establish effective service, education, support, and program delivery systems. The investigation should also facilitate development of MCI-specific interventions to address the needs of couples before they encounter severe disease progression and more stressful caregiving conditions. *(Dr. Roberto and colleagues may be contacted at 540/231-7657)*

UVA Timothy Salthouse, Ph.D. (Department of Psychology) “Detection of preclinical Alzheimer’s disease”

Because an effective treatment for Alzheimer’s disease will likely have the greatest chance of success before the disease has progressed, there is a great deal of interest in achieving the earliest detection. Previous research has found that many individuals who are subsequently diagnosed with AD exhibit a pronounced decline in memory and other cognitive abilities in the years immediately prior to diagnosis.

This project will conduct longitudinal retesting of adults over 70 years of age who provided cognitive and psychological data one to three years previously. Individuals will be classified as intact or impaired at the time of retesting on the basis of scores from a global screening measure (the Mini Mental Status Exam). The sensitivity and specificity of the prediction, as well as changes in a variety of self-reported psychosocial variables designed to assess depression, anxiety, and personality will be evaluated. (*Dr. Salthouse may be contacted at 434/982-6323*)

VCU Shijun Zhang, Ph.D. (Department of Medicinal Chemistry) and Tailiang Guo, Ph.D. (Department of Pharmacology and Toxicology) “Bivalent ligands targeting amyloid- β -peptide and lipid rafts”

A growing body of evidence has recognized small, soluble oligomers of A β , rather than the insoluble A β fibrils, as the major toxic species for early cognitive impairment in patients with AD. Inhibition of A β oligomerization, then, represents an attractive approach for developing potential therapeutics. A number of small molecules (including curcumin, a natural product mainly used as a food coloring agent) have been discovered to disrupt this process. Yet, only a few have moved to clinical trial due to their low *in vivo* potencies in blocking A β oligomerization or aggregation. Recently, convincing evidence has implicated the important role of lipid rafts, the highly packed microdomains in cell membrane, in facilitating A β oligomerization and toxicity. Although not completely understood at this stage, it is hoped that this relationship can be exploited to develop novel and potent A β oligomerization inhibitors. The investigators propose that a bivalent ligand containing an A β -binding moiety and a lipid raft-anchoring moiety will function as a novel A β oligomerization inhibitor. By chaperoning the A β -binding moiety into lipid rafts, the bivalent ligand’s necessary steric interference to disrupt A β -A β interaction will be enhanced. Specifically, the study will design, synthesize, and biologically characterize a series of bivalent ligands containing curcumin and 3 β -cholesterylamine connected through a linker. The investigators will optimize the linker, the linker length, and the linker attachment positions on curcumin and evaluate the bivalent ligands’ ability to inhibit A β oligomerization in *in vitro* assays. (*Dr. Zhang may be contacted at 804/628-8266; Dr. Guo may be contacted at 804/828-6732*)

2008-2009 Awards Committee

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