

Alzheimer's and Related Diseases Research Award Fund

**FINAL PROJECT REPORT SUMMARIES FROM THE
2008-2009 ALZHEIMER'S RESEARCH AWARD FUND**

The Alzheimer's and Related Diseases Research Award Fund (ARDRAF) was established by the Virginia General Assembly in 1982 and is administered by the Virginia Center on Aging at Virginia Commonwealth University. Summaries of the final project reports submitted by investigators funded during the 2008-2009 round of competition are given below. To receive the full reports, please contact the investigators or the ARDRAF administrator, Dr. Constance Coogle (ccoogle@vcu.edu).

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

This investigation pursues the long term objective of developing new therapeutics that slow or arrest the clinical progression of the Alzheimer's disease (AD) by preventing the formation of plaques in the brain. The build up of A β in the brain, by cleavage of the amyloid precursor protein (APP), is thought to be a major mechanism for the disease. A β is formed by the action of β secretase (BACE1 or Beta-site amyloid cleaving enzyme) on APP. Using the enzyme to assemble its own inhibitor through *in situ* and copper catalyzed click chemistry, over 150 new compounds were investigated in this study to identify new potent and effective BACE1 inhibitors. Although eight compounds were found to inhibit BACE1 with moderate potency, they were not deemed sufficiently effective to merit further investigation in more sophisticated AD models.

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

Old Dominion University Gianluca De Leo, Ph.D. (School of Medical Lab & Radiation Sciences) "Improving quality of life and short-term memory loss in patients with Alzheimer's dementia: Smartphone application for capturing daily life moments"

This project was intended to determine if a slide show comprised of a set of daily life moments captured by a smartphone could improve the short term memory of patients with Alzheimer's disease. The study examined the feasibility of carrying the smartphone using a lanyard and software applications for capturing images automatically every five minutes during the day. Images collected during the first week were combined into a slide show and saved on a DVD that was viewed for four continuous weeks. The study provided positive satisfaction/usability results and evidence of an increase in the number of events remembered after seeing the slideshow. *(Dr. De Leo may be contacted at 757/ 683-6733)*

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"

Two enzymes are known to generate the A β protein deposits, BACE1 and γ -secretase. In addition to this action on APP, BACE1 and γ -secretase also cleave the sodium channel auxiliary subunits, β 1- β 4. A consequence of this cleavage for one of the β subunits is a reduction in the sodium channel surface expression levels, and in other studies, the activity of sodium channels was also altered. Sodium channels play a major role in the neuronal excitability responsible for the generation and conduction of electrical signals in the brain (i.e., action potentials). Since β subunits are important for fine tuning this activity, their cleavage could play a role in the progressive dementia associated with AD. This study showed that β 3 co-expression in cultured hippocampal neurons resulted in changes in the activity (gating) of expressed sodium channels and a decrease in the total sodium channel current. These changes in activity likely accounted for the increases in activity of the neurons. Neurons expressing β 3 had altered membrane properties and a higher action potential firing frequency than non-transfected neurons. Continuing studies to examine the effects of BACE1 and γ -secretase inhibitors are underway.

(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 activities of daily living and personal relationships, preliminary studies of effects on patients' families suggest a notable impact. This investigation assessed the daily frequency and intensity of the behavioral symptoms and challenges of persons diagnosed with MCI, examining associations with the psychological and physical health and well-being of their spousal care partners. Significant fluctuations in symptoms, behaviors, and outcomes for the care partners across days (within-person variation) as well as across individuals (between-person variation) were documented. Problem behaviors had a significant influence on the positive or negative outlook of care partners and on their marital interactions. On days when care partners experienced more stressors in situations not concerning the person with MCI, they reported more physical health symptoms. In contrast, on days when care partners reported memory-related problems in their spouses, they had higher levels of salivary cortisol and alpha-amylase. These atypical, stress-related hormone reactions may put the care partners' physical health at greater risk. Significant differences across care partners suggest that various types and levels of interventions will be effective according to the needs and personal characteristics of the care partners. *(Dr. Roberto et al. 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. This research project capitalized on the infrastructure developed with an NIH-funded project to investigate cognitive and psychosocial predictors of cognitive decline in adults under and over 70 years of age. Individuals were classified as intact or impaired at the second occasion of testing on the basis of scores from a global screening test, the Mini-Mental Status Exam (MMSE). Analyses employing a battery of sensitive cognitive variables and a variety of self-report psychosocial measures of depression, anxiety, and personality were conducted to identify predictors of status at the second occasion, as well as changes in MMSE scores across occasions. Although MMSE scores were found to be related to reasoning and vocabulary abilities in adults of all ages, significant change in MMSE was associated with significant reductions in memory ability only among adults over 70 years of age. Declining memory appears to be one of the most sensitive indicators of late-life cognitive impairment, while other cognitive abilities or psychosocial variables may not be indicative at all. *(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”

Although the etiology of AD remains elusive, the amyloid hypothesis has long been the dominant explanatory theory. Recently the consensus recognition of soluble A β oligomers as the major toxic species has made A β oligomerization an attractive target in the development of effective AD treatments. Recent convincing evidence has implicated the important role of lipid rafts, the highly packed microdomains in cell membrane, in facilitating A β oligomerization and toxicity. In addition, a number of small molecules (including curcumin, a natural product mainly used as a food coloring agent) have been discovered to disrupt this process, although no strategically distinct A β oligomerization inhibitors are currently available. The goal of this research was to: 1) optimize the linker, the linker length, and the linker attachment positions on curcumin, and 2) evaluate a series of bivalent multifunctional ligands (BMFLs) containing curcumin and cholesterol analogs connected through a linker. Results from these preliminary studies indicate that: 1) the C-4 position on curcumin is optimal for producing favorable A β oligomerization inhibition; 2) the cell membrane anchor pharmacophore with basic nitrogen connected to the spacer is important; and 3) the spacer length is an important structural determinant for A β oligomerization inhibition. Ultimately, the development of these novel chemical tools will help the investigators unravel the role of A β oligomers in the pathogenesis of AD. *(Dr. Zhang may be contacted at 804/628-8266; Dr. Guo may be contacted at 804/828-6732)*