

Alzheimer's and Related Diseases Research Award Fund

**FINAL PROJECT REPORT SUMMARIES FROM THE
2007-2008 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 2007-2008 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).

VCU Galya R. Abdrakhmanova, M.D., Ph.D. (Department of Pharmacology and Toxicology, School of Medicine) "Novel Epibatidine Analogs as Potential Selective Agonists of $\alpha 4\beta 2$ nAChRs"

Neuronal nicotinic acetylcholine receptors (nAChRs) expressed in the brain are known to be important for cognition, learning and memory, and their deficiencies are shown to play a crucial role in Alzheimer's disease (AD) pathogenesis. Neuronal nAChRs consist of various combinations of $\alpha 2$ - $\alpha 10$ and $\beta 2$ - $\beta 4$ subunits. The most abundant subtypes of nAChRs in the central nervous system are $\alpha 4\beta 2$ and $\alpha 7$, whereas $\alpha 3\beta 4$ predominates in the periphery. Administration of nAChR agonists with high affinity to the $\alpha 4\beta 2$ nAChR has been proposed as one of the approaches for the treatment of AD. Further, the activation of $\alpha 7$ nAChRs has been recently shown to exhibit a neuroprotective action. The natural alkaloid epibatidine is known to possess a high affinity but lack of selectivity towards central neuronal nAChRs. Three novel analogs of epibatidine with -Cl, -F or -NH₂ substitutions at the 3' position of the pyridine ring, that have been recently developed and found to possess high binding affinity to brain nAChRs, were proposed to be tested: a) *in vitro* for their functional activity and nAChR subtype selectivity; and b) *in vivo* for a memory enhancement effect. The *in vitro* patch-clamp experiments demonstrated that, compared to the two other tested analogs, 3'-fluoro substitution in the epibatidine pyridine ring results in an analog with the most effectively increased efficacy and improved selectivity for $\alpha 4\beta 2$ versus $\alpha 3\beta 4$ nAChRs, while retaining an agonist effect on $\alpha 7$ nAChRs. These findings suggest that 3'-fluoro analog of epibatidine may serve as a novel candidate for a treatment of AD due to its potential memory enhancement, neuroprotection and minimized peripheral side effects. The *in vivo* studies were still in progress due to a temporary failure of positive nootropic control compounds to decrease the number of errors in the radial arm maze test. Continued work aims to replicate the nootropic effects of donepezil and rimonabant in the radial arm maze test, in order to proceed with evaluation of the novel 3'-fluoroepibatidine analog for memory enhancement. **(Dr. Abdrakhmanova can be reached at 804/828-1797)**

Shenandoah Mary A. Corcoran, Ph.D., OTR (Div. of Occupational Therapy, School of Health University Professions) "Caregiving Styles of Adult Children Who Provide Dementia Care"

Thirty one individuals who provide care for a parent or similarly related person with dementia participated in this qualitative study of caregiving styles. Each participant was interviewed on three occasions (for an average of 55 minutes per occasion) and completed a questionnaire to gather information about sociodemographic characteristics and well-being. With regard to the elements of caregiving style (beliefs, meanings, and actions), filial caregivers reported a consistent set of beliefs about the nature, causes, and progression of dementia and the definition of an ideal caregiver (although most would not claim to embody that definition). Meanings associated with caring for a parent included priorities for care (trying to avoid future regrets, paying respects to an honored parent, and fulfilling commitments), costs, conflicts, self-image, and change. Actions included interacting with the parent (i.e., communication, managing medical routines, being vigilant), managing the system and environment (i.e., interacting with the staff at an assisted living facility or keeping things organized), and managing self and non-parental responsibilities (i.e., work duties and children). Turning to overall style, it was found that the context of care is an important factor in determining style, with the presence of other involved family members and living arrangement shaping patterns in thinking and action. Three caregiving styles have emerged 1) Informing – collecting and dispensing information about the parent and from the literature to influence the care decisions of others; 2) Arranging – juggling multiple roles and schedules including caregiving; and, 3) Monitoring and Managing – being vigilant about the health of the parent and acting on his/her behalf with formal care providers. **(Dr. Corcoran can be reached at (540/665-5563)**

UVA Erik J. Fernandez, Ph.D. (Department of Chemical Engineering) “Designed Peptides as Models for Amyloid- β Toxicity”

Alzheimer's disease has long been known to involve formation of fibrillar structures from a protein fragment termed amyloid- β . More recently, the interactions between this protein fragment and cell membranes have been implicated as critical aspects to the neuronal damage in Alzheimer's patients. This research demonstrated that a peptide mimic of the amyloid- β peptide can exhibit many of the critical features of A β behavior, including self-association, binding to membranes, and acceleration of self-association by membranes. Particularly important, the mimic is also toxic to neurons. Further, like A β it shows the trend that intermediate concentrations of the peptide are most toxic. This suggests that at least some aspects of the disease may be valuably studied using such peptide mimics. Finally, the investigators have also studied the effect of some recently discovered molecules that manipulate the aggregation of amyloid- β . They have been able to distinguish the effects of these molecules on peptide association vs. membrane binding. The results may have implications for the design of new therapeutic molecules that can prevent the toxic interactions of amyloid- β with membranes. *(Dr. Fernandez can be reached at 434 924-1351)*

VCU Richard A. Glennon, Ph.D. (Dept. of Medicinal Chemistry, School of Pharmacy) “Positive Allosteric Modulators of Cholinergic Receptors”

Alzheimer's disease is related, in part, to a deficiency in the neurotransmitter acetylcholine in relevant brain areas. Acetylcholine activates several types of brain receptors, and one current treatment modality is to prevent the degradation of acetylcholine by agents that block its metabolism (i.e., cholinesterase inhibitors). This “shotgun” approach can lead to undesirable side effects. Another approach would be to activate selected acetylcholine receptors using a novel agent. There are growing implications for the involvement of the nicotinic acetylcholine (nACh) receptor type. Unfortunately, there are multiple subtypes of these receptors making it difficult to specifically target the particular receptor subtype of interest. A natural product, desformylflustrabromine (dFBr), isolated in small quantities from a marine organism, was found to potentiate the effects of ACh. But, it does so through a unique mechanism that does not involve direct receptor activation (i.e., it is a positive allosteric modulator). Being the first member of a novel mechanistic type of agent that selectively activates the actions of ACh at the target nACh receptor subtype of interest (i.e., $\alpha 4\beta 2$ nACh receptors), it offered a new target for exploitation. The purpose of this work was to a) synthesize a sufficient quantity of dFBr as a water-soluble salt for pharmacological study, and b) identify which structural features are important for activity. The first goal was achieved, and structural features important for the potentiating action were identified. NIH funding is now being sought in order to utilize the information obtained so that activity might be optimized. *(Dr. Glennon can be reached at 804/828-8487)*

2007-2008 Awards Committee

John W. Bigbee, Ph.D.

Virginia Commonwealth University

Dusan Bratko, Dr. Sci.

Virginia Commonwealth University

Frank J. Castora, Ph.D.

Eastern Virginia Medical School

Jorge Cortina, M.D.

Hampton VA Medical Center

Anca D. Dobrian, Ph.D.

Eastern Virginia Medical School

Jeffrey L. Dupree, Ph.D.

Virginia Commonwealth University

Kathleen Fuchs, Ph.D.

UVA Health System

Douglas M. Gross, Ph.D.

College of William & Mary

Glen E. Kellogg, Ph.D.

Virginia Commonwealth University

Myra Owens, Ph.D.

Virginia Commonwealth University

Russell H. Swerdlow, M.D.

UVA Health System

Catherine J. Tompkins, Ph.D.

George Mason University

Beverly A. Rzigalinski, Ph.D.

Via College of Osteopathic Medicine

Virginia Tech