

Alzheimer's and Related Diseases Research Award Fund

2007-2008 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 (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. The ARDRAF competition is administered by the Virginia Center on Aging at Virginia Commonwealth University in Richmond. The five grant awards for 2007-2008 are as follows:

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) 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, $\alpha 4\beta 2$ and $\alpha 7$, are known to be important for cognition, learning and memory, and their deficiencies play a crucial role in Alzheimer's disease (AD) pathogenesis. Administration of nAChR agonists with high affinity to the $\alpha 4\beta 2$ nAChR is proposed as one of the approaches for a treatment of AD. The investigator has collaborated with others to develop potent novel epibatidine analogs that may be $\alpha 4\beta 2$ subtype-selective agonists of nAChRs. The specific aims of this project are to investigate this functional activity and then test a lead analog *in vivo*. Patch-clamp technique will be used to establish functional potency, efficacy, desensitization profile, and nAChR subtype selectivity. The identified lead analog will be investigated for nootropic or "smart drug" effects in a rat memory model. This combined experimental approach will serve to identify potential agents that can be used for a treatment of AD through selective agonist effect on $\alpha 4\beta 2$ nAChRs. (*Dr. Abdrakhmanova can be reached at 804/828-1797*)

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

This qualitative study is designed to describe the caregiving styles of filial caregivers who are providing care at home for a parent or parent-in-law with Alzheimer's disease or a related disorder. Caregiving styles are defined as the patterns in thinking and action that guide daily care decisions. Lack of information about filial care styles undermines the ability to develop targeted interventions for adult children that effectively and efficiently promote behavioral change. Thus, understanding the underlying structure of thinking and action (caregiver style) will support development of a just-right fit between the needs and preferences of the caregiver and the mechanisms of action in a behavioral intervention. The study will clarify the context of filial caregiving, support the next generation of caregiver interventions that build on naturally occurring caregiver styles, and support the development of caregiver-centered interventions for adult children that facilitate caregiving and promote care recipient function.

(*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"

The amyloid- β (A β) peptide self-associates to form oligomers and ultimately fibrils that are a molecular hallmark of Alzheimer's disease. In recent years, increasing evidence implicates aggregates rather than fibrils as the most neurotoxic species. Further, it appears that A β aggregates can bind to membranes in a way that depends on their oligomerization state. This investigator hypothesizes that A β oligomers will bind with a strength correlated with their neurotoxicity, and that binding will lead to an alteration in the distribution of oligomers. The study will apply a new deuterium labeling technique monitored by mass spectrometry to monitor changes in oligomeric structure in the presence of lipid bilayers. Further, the study will investigate a new set of model peptides that self associate and interact with membrane that may prove useful for studying the effect of controlled changes in oligomerization state and oligomer chemical properties on membrane oligomer interactions and neurotoxicity. (*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”

The cholinergic theory associated with Alzheimer’s disease contends that enhanced acetylcholinergic (ACh) neurotransmission can improve these processes. Impeding the metabolic degradation of ACh (via administration of cholinesterase inhibitors) and administration of agents that can mimic the effect of ACh are two approaches to treat Alzheimer’s disease. A particular subtype of ACh receptor implicated in the processes of memory and cognition, the $\alpha 4\beta 2$ nACh receptor, is a prime target for medications development. But, to date, no selective $\alpha 4\beta 2$ nACh receptor agonists have been identified. The concept of “allosterism” offers an altogether different and unique approach to circumvent this problem and provides a means to activate ACh channels without directly targeting the ACh receptor itself. An allosteric site is one that is distinct from the site to which neurotransmitter normally binds. A general drawback of this approach that normally stymies its utility is related to the structural uniqueness of the site; that is, because allosteric sites are different from the normal receptor site, there is usually no available information on how such an agent can be designed. The first selective $\alpha 4\beta 2$ nACh receptor positive allosteric modulator (dFBr) recently has been isolated from natural sources. The investigator’s laboratory has just achieved the first chemical synthesis of this agent and has confirmed its ability to increase ACh-induced channel currents. This study will optimize this novel lead by determining which structural features are required for activity by synthesis of structural analogs and an evaluation of their ability to activate $\alpha 4\beta 2$ nACh receptor channels. *(Dr. Glennon can be reached at 804/828-8487)*

UVA Isaac G. Onyango, DVM, Ph.D. (Department of Neurology, School of Medicine)
“Receptor for Advance Glycation End Products (RAGE) and Lipid Rafts Mediate Amyloid β Neurotoxicity”

In sporadic AD (sAD), increased $A\beta$ levels may derive from oxidative stress-mediated upregulation of β -secretase (BACE) activity. If valid, this scenario provides a mechanism for a reinforcing neurotoxicity, which includes $A\beta$ as a critical component but does not force acceptance of its primacy in the evolution of AD. Mitochondria have emerged as a potential major organelle site of $A\beta$ neurotoxicity, with direct access to endogenously produced $A\beta$. Recent studies indicate that the receptor for advanced glycation products (RAGE) serves as a membrane receptor for exogenous $A\beta$. This investigator has observed that exogenous $A\beta$ added to cells leads to a translocation of plasma membrane RAGE from its lipid raft localization to mitochondria. This observation provides a mechanism by which RAGE could mediate mitochondrial toxicity of exogenous $A\beta$ and provides a focus on mitochondria as the organelle mediating $A\beta$ neurotoxicity from both endogenous and exogenous sources. Because mitochondria are the source of most oxidative stress, in this paradigm $A\beta$ serves as a toxic signaling molecule that magnifies mitochondrially generated oxidative stress within neurons and communicates it to other neurons that may initially have lower endogenous $A\beta$ burden. *(Dr. Onyango can be reached at 434/243-5899)*

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