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 along a variety of avenues, such as the causes, diagnosis, and treatment of the disorder; public policy and financing of care; and the social and psychological impacts of the disease upon the individual, family and community. The ARDRAF competition for these pilot study funds ($16,500) is administered by the Virginia Center on Aging at Virginia Commonwealth University in Richmond.

UVAThomas C. Foster, Ph.D., Department of Psychology, "Mechanism for Memory Impairment and Pathophysiology Associated with Aging and Alzheimer's Disease"
Calcium is involved in the signal transmission between nerve cells. In turn, the transmission of information between these cells is required for memory. There is ample evidence for disruption of calcium regulation in aging and age-associated neuropathologies such as Alzheimer's disease. Our work indicates that changes in the calcium-dependent processes for neuronal signaling are altered during aging and are associated with memory impairments similar to those observed early in the clinical course of the disease.

Using aging rats as a model, our research indicates that changes in the electrical transmission properties of the brain and age-related impairments in memory can be reversed by treatments that block calcium entry into brain cells. This raises the possibility that future pharmacological interventions might be devised to act on calcium dependent processes for the prevention or treatment of age-associated neurological disorders.

EVMSEvan T. Keller, D.V.M., Ph.D., Glennan Center for Aging, and Paul F. Aravich, Ph.D., Department of Anatomy and Neurobiology, "Do Free Radicals Induce Interleukin-6 Expression in the Rat Hippocampus? A Model for Alzheimer's Disease"
Alzheimer's disease (AD) is a progressive degeneration of the brain that leads to dementia and death. The cause of AD is unknown, but levels of a protein called interleukin-6 (IL-6) are elevated in the brains of patients with AD. Because IL-6 both stimulates inflammation and increases production of the amyloid protein associated with AD, it may play a key role in the development of AD. The cause of high IL-6 levels in the brain, in turn, is unknown, but chemical substances called free radicals may contribute to this. Free radicals are chemicals that damage fats, proteins and genes. They increase with age and increase IL-6 levels in many different tissues. Free radicals are elevated in the brains of AD patients and may also contribute to the development of AD.

We believe that free radicals contribute to the development of AD by increasing IL-6 levels in the brain. To examine this possibility, we treated rats with high levels of oxygen to increase free radical activity in their brains. We then measured IL-6 protein levels in the hippocampal region of the brain. We found that IL-6 levels were increased by free radicals in the hippocampus. This information suggests that inhibiting IL-6 production in the brain may prevent or slow the development of AD.
EVMSFrancis J. Liuzzi, Ph.D., Department of Anatomy and Neurobiology, "Does Estrogen Protect Basal Forebrain Neurons from Neurodegenerative Changes?"

There is growing scientific evidence that estrogen plays an important role in brain development. The evidence suggests that neurons of the basal forebrain, a region implicated in memory and learning, may depend on estrogen during development. More recent data, from a number of laboratories, suggest that the dependence of basal forebrain neurons on estrogen may extend into adulthood. In humans, degenerative changes in these neurons have been implicated in Alzheimer's disease. Interestingly, in a small group of women Alzheimer's patients, estrogen replacement improved cognitive function.

In our laboratory, we have used ovariectomized adult female rats as a model of menopause. Removal of the ovaries depletes virtually all estrogen in the body. We had shown, in the sensory neurons of these animals, that estrogen had dramatic effects on one neuronal gene in particular, the neurofilament gene. This gene is essential for the maintenance of the neuron's cell body and processes. If the expression of this gene decreases, the neurons and their processes shrink and they become non-functional.

In the ARDRAF funded research in our laboratory, we examined the effects of estrogen replacement on basal forebrain neuronal expression of the neurofilament gene. We expected that a loss of estrogen would cause a decrease in the expression of this gene in basal forebrain neurons and their consequent shrinkage. We found, however, no difference in neurofilament gene expression between the untreated and the estrogen replaced animals. Our data suggest that basal forebrain neuronal neurofilament gene expression is not dependent on estrogen alone and that loss of other factors, such as nerve growth factor, in combination with a loss of estrogen, may play a role in the decline of basal forebrain neurons.

UVARussell H. Swerdlow, M.D., Dept. of Neurology, UVA Health Sciences Center, "Cytochrome Oxidase Associated Pathophysiology in Alzheimer's Disease"

Work funded by the Alzheimer's and Related Disease Research Award Fund of the Commonwealth of Virginia now provides insight into altered cell functioning in Alzheimer's disease. This research helps scientists understand why brain cells degenerate in this disease, and may also apply to other related diseases of the aged nervous system, such as Parkinson's disease and amyotrophic lateral sclerosis (Lou Gehrig's disease).

This work explored the status of mitochondria in Alzheimer's disease patients. Mitochondria are important components of most cells of the body and are responsible for cell respiration and energy generation. For over a decade, scientists knew that mitochondria were abnormal in persons with Alzheimer's disease, but were not sure why. This research indicates that at least some degree of mitochondrial dysfunction in Alzheimer's disease is related to disruption of specific genes located within the mitochondria proper. These genes carry the blueprints for constructing an important cell respiration enzyme called cytochrome oxidase.

Although it is not yet clear why these mitochondrial genes are disrupted, the consequences are profound. In addition to diminished functioning of cytochrome oxidase, mitochondria in Alzheimer's patients appear to act as free radical generators and disrupt communication switchboards within cells. Because of this, cells become fragile and die when provoked in ways that healthy cells easily tolerate.

On an optimistic note, some of this work demonstrates that, under experimental conditions, certain compounds can help limit the damage caused by mitochondrial dysfunction. This suggests that the development of drugs that act upon mitochondria may one day prove useful in the treatment of Alzheimer's disease.
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 along a variety of avenues, such as the causes, diagnosis, and treatment of the disorder; public policy and financing of care; and the social and psychological impacts of the disease upon the individual, family and community. ARDRAF conducts an annual competition for pilot study awards of $16,500 each, administered by the Virginia Center on Aging at Virginia Commonwealth University.

VCU/MCVJ. James Cotter, Ph.D., "Special Care for Persons with Alzheimer’s Disease or Related Disorders: The Response of Virginia’s Nursing Facilities, Adult Care Residences, and Home Care Agencies"

Long-term care organizations are responding to the new challenges of serving older persons with dementia by establishing Special Care Units (SCUs) and Special Care Programs (SCPs). Our study, the Continuum of Special Care Project, surveyed 301 nursing facilities, 584 adult care residences and 422 home health care agencies in Virginia to determine how many and what kind of SCUs and SCPs were being implemented and what types of organizations were initiating SCUs and SCPs. One in five nursing homes and adult care residences has an SCU or SCP. Nursing facilities serve an average of 39 residents in the SCUs; adult care residences served an average of 16 residents in their SCUs. Based on the facilities’ plans, 33% of these facilities will have established an SCU or SCP within the next two years. Nursing facilities and adult care residences that are larger, part of chains, in urban areas, and/or with affiliations to other providers, have a greater tendency to establish special care units than do other facilities. Most of the SCUs have a number of the key characteristics associated with special care units and programs, but only 14% have the full range of traits that characterize special care. Initiatives in home health agencies are nascent and focus on training and assignment of aides. Responses indicate considerable interest and experimentation on the part of long-term care organizations in Virginia to better serve persons with Alzheimer's disease or related dementia. (Dr. Cotter can be reached at 804/828-6938).

VA TechBradley G. Klein, Ph.D. and Jeffrey Bloomquist, Ph.D., "Improved Visualization and Localization of the Neural Substrates of Experimental Parkinsonism"

Parkinson's disease is a debilitating movement disorder of the brain which afflicts at least 1 million Americans in late middle age. It is analogous to Alzheimer's disease in its clinical target population, progressive neurodegenerative nature, and its functional, emotional and economic impacts upon the family and society. A condition almost identical to Parkinson's disease can be experimentally produced in animals by a compound called MPTP, which is similar in chemical structure to the herbicide paraquat. Although the MPTP model has provided important information on the neural mechanisms of Parkinson's disease, it is difficult to localize the regions and cells in the brain that use MPTP to produce the hallmarks of the disease. This research project addressed the usefulness of a chemical analog of MPTP, called t-THP, with regard to its potential for providing direct visualization of the brain regions and cells that are involved in experimental Parkinsonism. In general, results support several important similarities in metabolism, kinetics, and neurochemical function between MPTP and t-THP. However, one important difference demonstrated by our ARDRAF data, is that the \textit{t-P+} pyridinium metabolite of \textit{t}-THP does not appear to rely on sodium-dependent membrane transporters for incorporation into nervous system elements. It appears that \textit{t}-THP has promise for use as a visual marker for micro-environments where MPTP-like compounds are taken and converted to potentially neurotoxic pyridinium species. The utility of this marker is further underscored by our ARDRAF-funded finding that \textit{t}-THP does not appear to destroy components of the system it is meant to identify. Such a marker could be employed to address some of the issues regarding the selectivity of MPTP neurotoxicity. (Drs. Klein and Bloomquist can be reached at 540/231-7398)
Numerous experiments indicate that increasing the blood glucose level improves memory in patients with Alzheimer's disease. Glucose, which is the main fuel for the brain, can cross the blood-brain barrier and enter the brain. What happens to brain activity when blood glucose levels are raised has yet to be definitively determined. A new technology called Functional Magnetic Resonance Imaging (fMRI) allows researchers to examine brain activity while patients are performing memory tasks. In this study, brain activity was compared in Alzheimer's patients and healthy elderly people. Each participant had a functional MRI with high blood glucose levels on one occasion and normal blood glucose levels on another. While undergoing the fMRI, they performed tests of memory for stories and faces. Significant and novel results indicate that glucose improves memory for healthy elderly and people with Alzheimer's disease, and that the critical brain areas involved are similar. In addition, glucose has a direct effect on brain activity in both groups of people. (Drs. Manning and Downs can be reached at 804/982-1012)
Alzheimer's and Related Diseases Research Award Fund

FINAL PROJECT REPORTS FROM THE 1999-2000 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 along a variety of avenues, such as the causes, diagnosis, and treatment of the disorder; public policy and financing of care; and the social and psychological impacts of the disease upon the individual, family and community. ARDRAF conducts an annual competition for pilot study awards (currently $25,000 each), administered by the Virginia Center on Aging at Virginia Commonwealth University.

GMU Giorgio Ascoli, Ph.D. (Krasnow Institute), "Effect of Dendritic Morphology on Neuronal Electrophysiology in a Lesion Model of Alzheimer's Disease"

An important neurobiological marker of Alzheimer’s disease (AD) is the loss of neuronal cells and connections in the hippocampus. Because this brain structure is involved in memory formation, hippocampal damage has been the focus of animal models of AD. In particular, kainate lesions in the rat have been shown to reproduce anatomical (dendritic elongation and branch loss) and biochemical (spread receptor distribution) correlates of AD. This proposal explored the hypothesis that altered dendritic morphology, in itself, causes the drastically impaired electrophysiological behavior of nerve cells that is fundamental to memory loss and dementia. The investigator adopted an identical biophysical model to examine the potential interaction between the anatomical and physiological effects of kainate lesions in hippocampal neurons, characterizing the kainate-induced modifications of pyramidal cell dendritic morphology as well as the electrophysiological changes induced by these anatomical modifications. Results indicated that, although the kainate-lesioned neurons are structurally different from both young and aged control neurons, the electrophysiological behavior emerging from these three groups is much less differentiated. In other words, changes in dendritic morphology similar to those observed in AD are sufficient to induce only minimal quantitative (and no qualitative) alterations of neuronal activity. The researchers concluded that the electrophysiological impairment observed in AD and kainate-lesioned neurons requires both anatomical and biochemical changes to be fully explained. The results indicate a need for more extensive studies and larger pools of neurons to shed light on the mutual interactions between morphological and biochemical influences on neuronal activity. (Dr. Ascoli can be reached at 703/993-4383)

UVA Suzanne Holroyd, M.D. (Dept. of Psychiatric Medicine) & Andrew Wolf, M.D. (Dept. of Internal Medicine), "Attitudes on Whether Physicians Should Tell Alzheimer's Disease Patients Their Diagnosis"

There is no established protocol to guide physicians who diagnose dementing illnesses such as Alzheimer's disease (AD) about informing patients of their diagnosis. There are multiple dilemmas and difficulties related to when and how to deliver the diagnosis that pose challenges for both clinicians and families. This study surveyed two groups regarding their attitudes towards being given the diagnosis of AD, elderly clinic outpatients without dementing illness and family members of patients with AD in the community. Responses from the clinic outpatients, who represent diverse racial and socioeconomic backgrounds, were compared to earlier data from predominantly white older adults residing in an upscale retirement community. Here, a significantly greater proportion of respondents in the more diverse sample indicated that they would prefer to be informed of the diagnosis (92% vs. 79.5%), even though significantly fewer of them reported having relatives or close friends with AD or a similar illness (21.5% vs. 48.7%). Surveys of the family members of patients with AD indicated that while the vast majority of caregivers had been told of the diagnosis, only half of the patients had been informed. More than three-quarters of respondents agreed that patients should be told when they are diagnosed with a disease that affects memory and thinking. The level of their care recipients' cognitive impairment distinguished between those who agreed and disagreed. The results of this study lend support to the guidelines recently released by the American Medical Association advocating that patients be directly informed when a dementing illness is diagnosed. (Drs. Holroyd and Wolf can be reached at 804/924-2241)
VA Tech  Shannon E. Jarrott, Ph.D. (Dept. of Human Development), "The Effects of Instrumental Assistance on Family Caregivers of Patients with Dementia"
Caring for an elderly relative with a dementing illness has consistently been associated with increased levels of overload and decreased well-being. Caregivers may turn to informal (family and friends) and formal (paid) sources for assistance with the care of their relative, but often with mixed results. The present study examined how the amount and types of help dementia family caregivers receive affected caregiver stress and well-being (e.g., depression, anger, overload, and worry). Rather than relying on subjective caregiver evaluations, this study utilized multiple objective measures of the nature and extent of assistance that urban and rural caregivers receive. Results indicated that higher baseline levels of formal, but not informal, help were associated with lower caregiver distress. Greater formal assistance with the activities of daily living (ADls) was the type of help most strongly associated with lower distress. Although gains in informal help across time were associated with lower depression, changes in the levels of formal help were not related to caregiver distress. Higher levels of conflict associated with formal helpers buffered the effects of increased formal assistance and resulted in higher caregiver distress. It is suggested that even mild conflict has an important negative effect on caregivers. Support programs that provide appropriate and acceptable assistance are warranted. (Dr. Jarrott can be reached at 540/231-5434)

UVA  Virginia Simnad, M.D. (Dept. of Neurology), "Alteration in Proton Spectra of the Hippocampus to Oral Ingestion of Glucose in Alzheimer's Disease"
Alzheimer’s disease is accompanied by atrophy or a decrease in brain tissue particularly in the hippocampus. Neurochemical changes also take place, although, until recently, it has been difficult to view these changes in living individuals. Magnetic Resonance Spectroscopy (MRS) is a new technology which identifies chemical activity in the brain in a safe non-invasive manner. This is accomplished using the same magnet that is used for magnetic resonance imaging (MRI) which identifies brain structures. This study examined chemical activity in the hippocampus, a brain area critically affected by Alzheimer’s disease. Significant differences were observed in the brain patterns exhibited by Alzheimer’s patients, healthy elderly, and healthy young people. N-acetyl-aspartate, a chemical associated with energy production and neuronal viability, was lowest in the Alzheimer’s patients, followed by somewhat higher levels among the healthy elderly, with highest levels of the compound in the healthy young participants. Current investigations are examining the relationship between cognitive functioning and chemical concentrations in the hippocampus. (Dr. Simnad can be reached at 804/243-5931)

VCU  Patricia W. Slattum, Pharm.D., Ph.D. & Vivien E. James, Pharm.D. (Dept. of Pharmacy and Pharmaceutics), "Anticholinergic Medication Use in Elderly Patients Diagnosed with Dementia or Taking Acetylcholinesterase Inhibitors"
Age- and disease-related changes in the cholinergic nervous system contribute to the functional decline, memory impairment and worsening quality of life observed in Alzheimer’s (AD) patients. Administration of anticholinergic medications could result in further adverse consequences in these patients. A wide variety of anticholinergic medications are used to treat conditions comorbid with AD, including Parkinson’s disease, incontinence, depression, abdominal cramps, and allergies. Acetylcholinesterase inhibitors, such as donepezil (Aricept®) and tacrine (Cognex®), increase levels of acetylcholine in the central nervous system and improve cognition in some patients with AD. Co-administration of central anticholinergic agents should counteract these effects, reducing the potential benefit of either agent. This study assessed the use of prescribed anticholinergic medications in a Medicare Supplemental insured population and in elderly patients treated in a large group family physician practice. Patients were evaluated for anticholinergic medication use and presence of AD or other dementia. Concurrent use of anticholinergics and acetylcholinesterase inhibitors was also determined. Review of insurance claims revealed that 12.0% of patients with dementia and 13.4% of patients taking acetylcholinesterase inhibitors received anticholinergic medications known to have significant effects in the central nervous system, compared to 10.0% of elderly patients without dementia. Review of charts in the group family practice showed that 41% of dementia patients and 56% of patients taking acetylcholinesterase inhibitors received a medication with some degree of anticholinergic effects, compared to 19% of elderly patients without dementia. Results of this study suggest that patients at high risk for anticholinergic adverse events, particularly those with dementia, continue to receive anticholinergic drugs inappropriately. Drug-drug interactions may be lessening the intended therapeutic effect of the Alzheimer’s medication. Increased attention to this problem is needed. (Drs. Slattum and James can be reached at 804/828-6355)

[To receive the 2000-2001 ARDRAF Call for Proposals please call the Virginia Center on Aging (804) 828-1525 and give us your name, mailing address, phone number, and e-mail]
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UVA      James P. Bennett, Jr., M.D., Ph.D. & Christine Thiffault, Ph.D. (Dept. of Neurology)
"Mitochondria Membrane Potential in Alzheimer's Disease"

It has been hypothesized that AD derives from dysfunctioning mitochondria in neurons, and that
abnormal mitochondrial genes are ultimately responsible for these defects. The investigators utilized a
reliable cell model (known as a "cybrid") that enables the abnormal mitochondrial genes of AD patients to
be examined in an intact cell, and studied the biophysiology of mitochondria in these cell models.
Cybrid mitochondria from non-AD subjects exhibit a cyclical loss and restoration of their membrane
charge. In the presence of a fluorescent dye, this appears under the microscope like blinking lights and is
called "flickering." Mitochondria inside cybrid cells made from AD patients do not flicker normally, and
this funded study showed that flickering is coupled to the flow of electrons in mitochondria, down what is
referred to as the electron transport chain. This is a complex group of proteins that mitochondria use to
synthesize ATP, a general source of cell energy. The investigators now believe that AD mitochondria
have defective coupling of electron flow to ATP formation, and this is why they fail to flicker normally.
The results of this study show that mitochondrial genes in AD produce defective energetics in
mitochondria. They also provide a potential means for identifying drug development targets: a drug
that could restore flickering to AD mitochondria would be expected to improve this coupling of energy
production. (Drs. Bennett and Thiffault may be contacted at 434/924-8374)

Goodwin House Sheila Caswell, Mary A. Corcoran, Ph.D, O.T.R., & Karen Love, B.S.
"A Staff-Developed Program to Enhance Care Quality for Residents with Dementia"

This project engaged 39 nursing home staff in designing high quality care for residents with dementia.
Staff were taught to use principles of care based on the Montessori educational approach for cognitive
development in children. These principles guided the staff to simplify both the physical environment and
everyday activities to match the abilities of each resident. By empowering facility staff to direct an
aspect of daily care, the investigators anticipated positive outcomes related to staff retention, quality of
care, and caregiving self-efficacy in comparison with nine control group participants at a separate but
similar facility who did not receive the intervention training. The results of inferential statistical analyses
using repeated measures are discussed as they relate to administrative cooperation and commitment, a
factor that is emerging in the literature to be crucial for successful staff programs. (Ms. Caswell and
colleagues may be contacted at 703/824-1167)

EVMS Barbara Freund, Ph.D., R.N. (Glennan Center for Geriatrics and Gerontology)
"Use of the Clock Drawing Test as a Screen for Declining Driving Competency in Cognitively
Impaired Older Adults"

The primary purpose of this study was to determine if the onset of declining driving ability can be
predicted by the Clock Drawing Test (CDT), a rapid, simple clinical measure of executive functioning in
older adults with cognitive impairment. A secondary purpose was to compare simulated driving
performance with actual on-road driving performance. Twenty nine men and women, aged 65 and older,
completed the CDT and a simulated driving test. In addition, nine of these subjects were randomly
selected to complete an on-road driving test. The findings demonstrate that the CDT is a useful screen
for driving competency, even among participants with only mild cognitive impairment. Results further
suggest that high fidelity driving simulation is a sensitive method to objectively evaluate driving
performance and may be a valid alternative to on-road testing. The results support the use of the CDT
by clinicians interested in determining when patients should be referred for driving evaluation. (Dr.
Freund may be contacted at 757/446-7040)
"Amyloid Beta Protein-Induced Hippocampal Cell Death: Mechanism of Action"

Amyloid beta protein (A beta) is a major constituent of plaques in AD and has toxic properties. The precise cellular and molecular mechanisms by which amyloid beta protein may induce neuronal cell death and injury have yet to be determined. The results of this study suggest that pretreatment with the neurosteroid, pregnenolone, or the estrogen antagonist drug, tamoxifen, protects HT-22 cells against A beta-induced cell death. Second, treatment with A beta resulted in enhanced nuclear localization of glucocorticoid receptors (GR) in clonal mouse hippocampal HT-22 cells as compared to control untreated cells (or pregnenolone- or tamoxifen-alone treated cells). Interestingly, prior pregnenolone or tamoxifen treatment followed by A beta resulted in dramatic reduction in GR nuclear localization. In addition, using pharmacological and biochemical approaches, the investigators showed that under in vitro conditions, A beta-induced cell death is mediated, in part, by the activation of protein kinase C (PKC), activation of mitogen-activated protein kinase (p38 MAPK), and modulation of inducible nitric oxide synthase (iNOS). (Dr. Kalimi may be reached at 804/828-9500)

"Percutaneous Endoscopic Gastrostomy (PEG) for Nutritional Support in Persons with Advanced Dementia and Feeding Difficulties: Do the Outcomes Fulfill the Expectations of the Decision-Maker?"

Eating difficulties are common in advanced dementia and family members may be faced with the difficult decision of whether to artificially maintain nutrition, which is usually done through a tube placed directly into the stomach by means of a PEG. Recent literature suggests that tube feeding rarely prolongs life, improves nutrition, or makes the patient any more comfortable, yet advanced dementia is still a major indication for PEG placement in Virginia. This study was designed to gain further insight into why the decision is made to place a PEG by interviewing the responsible family member (decision-maker) at the time of PEG placement and three months later. Results indicate that the majority of decision-makers expected tube feeding to prolong life, improve nutrition, decrease aspiration and improve comfort, and most hoped it would improve quality of life (QOL). Although the overwhelming reason given for PEG placement was to keep the patient alive, only 50% of patients survived three months. The decision-makers of the survivors stated that their expectations had largely been met. Subjective improvement in QOL was reported, but little evidence was offered to substantiate this. The investigators conclude that PEG placement in advanced dementia is largely a matter of treating the family, rather than the patient, and raise questions about whether this is ethically justified. (Dr. O'Keefe and colleagues can be reached at 804/828-5323)

"Tactile and Visual Stimuli in Alzheimer's Care Units: Incorporating Quilts in the Living Environment"

Careful design planning in facilities for individuals with Alzheimer's disease and other forms of dementia can provide environments beneficial to the well-being of residents. Important components in therapeutic settings are objects that provide cultural meaning, are stimulating to the touch, or reminiscent of things familiar in their previous homes. The purpose of this study was to examine the behavioral impact of hanging quilts in the public areas of Alzheimer's care facilities. The investigators were interested in determining if residents with AD would interact physically with the quilts or exhibit altered wandering behavior because of their interest and engagement with them. A modified behavioral mapping technique was employed in two facilities that differed in the amount of visual and textile stimuli available to the residents. The addition of quilts had little impact at the environmentally rich site, but had a dramatic affect in the facility that was previously poor in visual and tactile stimuli. Thequilts needed to be vertically lowered to be in the viewing plane, however, in order to achieve significant interest and interaction. Wandering behaviors were only modified to include the quilt manipulations into normal wandering patterns, and exiting behaviors were not diminished. This study, the first in a series to identify more fully appropriate components of the physical environment that can enhance quality of life, has implications for other types of stimulating or culturally meaningful objects in long-term care facilities. (Drs. Schofield-Tomschin & Marshall-Baker may be contacted at 540/231-3250)
UVA Erik J. Fernandez, Ph.D. (Department of Chemical Engineering)
"Revealing Amyloid-β Structure and Oligomer Distributions Using Mass Spectrometry"
Alzheimer’s disease has long been known to involve formation of fibrillar stuctures from a protein fragment termed amyloid-β. This protein fragment also forms smaller aggregates that recently have been implicated as the actual toxic species responsible for neuronal damage in Alzheimer’s patients. In this research, a new approach based on isotope labeling and mass spectrometry has been used to investigate the structure of amyloid β. The results indicate this technique should be useful in subsequent research to identify the toxic form of amyloid β and identify the structural features responsible for its toxicity. (Dr. Fernandez may be contacted at 434/924-1351)

UVA Carol Manning, Ph.D. and Kathleen Fuchs, Ph.D. (Department of Neurology)
"The Subjective and Objective Experience of Women at Genetic Risk for Alzheimer's Disease"
Concern about the onset of dementia is especially high among women with a parent diagnosed with AD. However, little research has been done to examine cognitive and emotional functioning in those who have first-degree relatives with AD. The investigators assessed the cognitive and emotional functioning of a group of women at increased risk for developing Alzheimer’s disease (AD) because they have a parent with AD, and compared their performance with women of comparable age and education who do not have a parent with AD. They found that the women at risk report more symptoms of caregiver burden and anxiety than their peers, but that their general cognitive functioning is comparable. The women in the at-risk group performed in the above average range on a measure of general memory functioning, but they did not perform quite as well as their peers. It does not appear that the difference in level of emotional distress accounts for the difference in memory performance. The investigators are currently investigating other aspects of performance such as learning characteristics that might account for this finding. (Drs. Manning and Fuchs may be contacted at 434/982-1012)

UVA John Savory, Ph.D. and Othman Ghribi, Ph.D. (Department of Pathology)
"Stress in the Endoplasmic Reticulum Mediates Active Neuronal Death in Experimental Neurodegeneration"
Recent studies have implicated apoptosis in the progressive and selective loss of neurons that characterizes AD. Although apoptosis under mitochondrial control has received considerable attention, the mechanisms utilized within the endoplasmic reticulum (ER) are not well understood. This project first investigated the neurotoxic effect of direct injection of Aβ1-42 into the brains of New Zealand white rabbits on the ER. Secondly, the researchers established that pre-treating animals with a molecule that up-regulates antiapoptotic protein levels in the ER, glial cell line-derived neurotrophic factor (GDNF), protects against Aβ1-42-induced neurotoxicity. The investigators further chose to use lithium treatment in an additional study, since recent work implicated mediation by activity in the glycogen synthase kinase-3β (GSK-3β) and MAP kinases (JNK, p 38, and ERK) signaling pathways. Lithium, used to treat bipolar disorder, was found to protect against Aβ-induced neurotoxicity and tau phosphorylation by mechanisms that may involve anti-apoptotic as well as GSK-3β regulation activities. The investigators made significant progress in understanding pathways by which the important Alzheimer’s peptide, Aβ, causes injury to neurons, and have pointed the way to possible treatments. (Drs. Savory and Ghribi may be contacted at 434/924-5682)
This research proposed to use: 1) scopolamine, a competitive cholinergic antagonist, to temporarily mimic the symptoms of AD in healthy elderly volunteers, and 2) physostigmine, an acetylcholinesterase (AChE) inhibitor used to treat AD patients, to reverse the cognitive impairment induced by scopolamine. The time course of reversal was determined by the physostigmine concentrations in blood achieved in each individual, and sophisticated PK/PD modeling was used to analyze cognitive functioning changes (mimicking AD symptoms), heart rate and saliva flow changes (known side effects of physostigmine), and blood concentrations of scopolamine and physostigmine. Overall, the AChE inhibition was mild (due to the relatively low dose of physostigmine, limited by concern about clinical adverse effects) and short-lived (due to the short half-life of the physostigmine administered). This was reflected in the small and transient reversal effects on the scopolamine-induced pharmacological effects. Higher physostigmine doses, given as an intravenous infusion, would be required to show a more profound and long-lasting (therapeutic) AChE inhibition reversal. However, the results do suggest that physostigmine reverses the scopolamine-induced effects consistent with its therapeutic effect in AD. In addition, the results suggest that elderly females are more sensitive to the effects of scopolamine and physostigmine relative to their male counterparts. (Drs. Venitz and Men may be contacted at 804/828-6249)

"Alzheimer's Disease Caregiver Occupational Performance, Respite as a Mental Break, and Program Implications"

Recent research suggests that caregivers of persons with AD need more than simple physical distance from care recipients to truly experience respite. Achieving a mental break is conceptualized as the essence of respite and as a restorative occupation. Caregivers need to feel free and confident that their loved ones are not just safe, but meaningfully engaged, so that they experience a mental break from their concerns. A phenomenological study involving four in-depth interviews each with fifteen family caregivers of persons with AD explored the experience of getting a mental break. This project produced a working model of how caregivers of persons with AD get a mental break. The model addresses associated factors including: Social Support, Traditional Respite (including Playing “Beat the Clock”), Relief Enhancing Conditions (including Caregiver Predispositions and Situational Prerequisites), and Techniques for Momentary Stress-Reduction (Relaxing Expectations and Getting Unstuck). Achieving a Mental Break addresses: Mental Break Techniques (Creative Deception and Caregiver Carpe Diem) and Experiencing a Mental Break (Absorbing Activities, Description of Mental Break, The Price You Pay). The last components are: Respite Impediment (The Challenge of Accepting Help) and Advice From Caregivers to Caregivers. Practical implications include: continuing refinement of formal respite services to facilitate a mental break by flexible scheduling and demonstrating staff compassion, competence, dependability to reassure caregivers and recipients; counseling caregivers about the other-serving (not self-serving) potential of a mental break to re-energize them in their caregiving roles; promoting the idea that refreshing breaks can be achieved through a wide range of absorbing activities that are mildly or totally absorbing, of short or long duration, near or far from the care recipient, and simple or complex. Further analyses of data from this study will be used to develop a specific psychoeducational intervention for assisting caregivers in identifying opportunities for and achieving mental breaks from their caregiving responsibilities. (Drs. Watts and Teitelman may be contacted at 804/828-2219)
FOR IMMEDIATE RELEASE – November 1, 2003

FINAL PROJECT REPORTS FROM THE
2002-2003 ALZHEIMER’S RESEARCH AWARD FUND

VA Tech  Paul R. Carlier, Ph.D. (Department of Chemistry) “Structure-Based Design of Dimeric Memory Enhancing Drugs”
Current FDA-approved therapies for alleviating Alzheimer’s memory loss are based on the use of enzyme inhibitors to increase the concentration in brain of the neurotransmitter, acetylcholine. Unfortunately, use of these drugs (acetylcholinesterase inhibitors) is accompanied by side effects which are largely caused by interaction with unintended biological targets. This study was designed to decrease side effects by improving selectivity for the enzyme of interest, acetylcholinesterase. In the project period the investigator synthesized new acetylcholinesterase inhibitors based on the active constituent of the Chinese medicinal herb, Huperzia Serrata (Huperzine A). The drug candidates synthesized in this project represent a second generation of dimeric Huperzine A-derived enzyme inhibitors and their design was informed by atomic scale pictures of how the synthesized drugs attach themselves to acetylcholinesterase. Each drug candidate contains two fragments of Huperzine A, and can thus interact with acetylcholinesterase at two points, attaining a “tighter grip.” This tighter grip will hopefully translate to lower therapeutic doses and lower occurrence of side effects. The second generation of drug candidates differs from the first in the use of a more rigid connector between the Huperzine fragments; the increased rigidity should result in greater inhibitory activity. The investigator is currently awaiting bioassay results to learn if the second generation of drug candidates offers superior potency. (Dr. Carlier can be reached at 540/231-9219)

VCU  J. James Cotter, Ph.D., E. Ayn Welleford, Ph.D. (Department of Gerontology) and Kathy Vesley-Massey (Chesapeake Bay Agency on Aging, Inc.) “Improving the Capacity of Home Care Aides in Rural Areas Serving Persons with Alzheimer’s Disease and Related Disorders”
Training for long-term care workers serving persons with Alzheimer’s disease and related disorders (ADRD), especially home care aides, is one of the most important challenges confronting the health care system. The investigators implemented two interventions (Training Only and Training with Support) to enhance rural home care aides’ skills in caring for persons with ADRD, and they measured the effect of the interventions on the aides, the informal caregivers (e.g. family), and the patient. They also explored the challenges and opportunities of collaborative research between an academic medical center and a community-based agency for older persons. Aides’ knowledge of Alzheimer’s disease increased substantially and was maintained over the course of the study. Despite a more impaired client, the Training and Support intervention was effective in maintaining high degrees of aide and caregiver satisfaction and decreasing the caregivers’ perceptions of burden. There were mixed effects for the Training Only group. The investigators identified a number of barriers and facilitators of success in conducting research with persons with ADRD in community-based settings, including the need to focus more resources on recruitment and retention of research participants. The researchers are currently investigating the effect of severity adjustment on outcomes and the potential for expanded community-based research studies to learn more about improving home care aide performance and client satisfaction. (Dr. Cotter and colleagues may be contacted at 804/828-6071)
UVA  Elana Farace, Ph.D. and Mark E. Shaffrey, M.D (Department of Neurological Surgery)  
“Neurocognitive Discrimination of Alzheimer's from Normal Pressure Hydrocephalus Verified by Brain Biopsy”
Many elderly patients with dementia are referred each year to neurosurgeons for evaluation and possible placement of a brain shunt to drain excess cerebral spinal fluid as a means of treating Normal Pressure Hydrocephalus (NPH), a disease characterized by dementia, gait problems, and urinary incontinence. NPH can be successfully treated with the use of a shunt, or tube which drains off the excess fluid. Approximately 10-30% of all patients who present with suspected NPH may have Alzheimer’s disease (AD), either as a separate diagnosis or at the same time that they have NPH. This study was intended to determine the effect of AD on whether or not NPH patients benefited from a shunt placement. The research showed that the true rate of AD in patients with presumed NPH undergoing shunt procedures was 40%, much higher than previously thought. These patients with AD tended to improve with shunt placement in terms of walking and urinary continence, but their dementia remained the same or worsened. Neuropsychological testing was diagnostically suggestive of NPH, and may contribute to a non-invasive method for determining possible NPH and AD. This research will lead to improved outcomes in patients appropriate for shunt placement in NPH, and help patients with AD avoid unnecessary neurosurgery.  
(Drs. Farace and Shaffrey may be contacted at 434/2434806)

JMU  Merle E. Mast, Ph.D. and Marylin Wakefield, Ph.D. (Department of Nursing) “Rural Family Caregivers’ Perceptions of Facilitators and Deterrents to the Use of In-Home Respite”
Although caregivers of persons with AD cite respite as a pressing need, many caregivers do not use respite services or delay using them until very late in the disease process. To date, research has noted, but has not gained, an understanding of this phenomenon. Little is known about the extent to which specific interventions correspond to caregivers’ perceptions of what they need and would find useful. This qualitative study used Grounded Theory to explore rural family caregivers’ perspectives of the factors that either enhance or deter the use of in-home respite. Emergent themes include family relationships, loss/grieving, trust, caregiver self-knowledge, caregiver purpose/role/sense of obligation, family/cultural taboos, decision-making process, seeking/asking for help, barriers to asking for help, and defining moments. Caregiver distress is a major over-arching theme, clustering in four distinct and interrelated areas: “normal” aging stressors, family issues, unresolved grief, and inadequate assistance. There seems to be an inverse correlation between the level of caregiver distress and the willingness to seek out, and accept, in-home respite services. Forthcoming results will provide definitions of caregiver distress and a working model of the interrelatedness of caregiver distress to decision-making about in-home respite care. 
(Drs. Mast and Wakefield may be contacted at 540/568-6314)

Mountain Empire Older Citizens, Inc.  Marilyn Pace Maxwell, M.S.W. and Michael Creedon, D.S.W  “Using the Internet for Alzheimer’s Care: The Challenge for Elders and Service Organizations in Approach”
The development of wired communities, broadly connected by computer technology, allows local organizations to interact with and support specific families and individuals in previously unexplored ways. Taking advantage of this progress in rural Southwest Virginia, the investigators examined the feasibility of computer-assisted support for family caregivers of persons with Alzheimer’s disease. A telephone survey of caregivers found that 50% of respondents had access and were willing to use computers as a learning tool and to support their caregiving roles, though few currently used computer technology as an information source. Few of those without access expressed any desire to use, or learn to use, computers. Three of the eleven participants in a focus group on electronic technology and caregiving were using computers for caregiving purposes (two for an Alzheimer’s chat room, one to access the Alzheimer’s Association web site). Most were willing to learn to use computers for caregiving, and all regarded teenage trainers as a positive resource. These findings serve as the basis for program development and technology support services, with the ultimate goal of assuring that the needs of Alzheimer’s caregivers are included in the region’s plans for developing the wired community.  
(Ms. Maxwell and Dr. Creedon may be contacted at 276/523-4202)
FINAL PROJECT REPORTS FROM THE
2003-2004 ALZHEIMER'S RESEARCH AWARD FUND

UVA James P. Bennett, M.D., Ph.D. and Bradley Miller, M.D., Ph.D. (Department of Neurology/Division of Neuropathology) "Mitochondrial DNA Deletions and Mutations in Alzheimer's Disease Brain Neurons"

This research examined the genetic contribution mitochondria make to Alzheimer's disease (AD). Several aspects of this neurodegenerative disease (i.e., largely sporadic incidence, increasing severity with age, proclivity for neuronal damage) mirror aspects of mitochondrial genetic disease. Until recently, though, it has not been possible to examine directly the mitochondrial DNA content of single neurons. This study has involved the application of a set of stains to identify neurons with either functional or non-functional mitochondrial electron transport chains (ETC, from which much of a neuron's energy currency [ATP] is generated), isolation of single neurons, and PCR (polymerase chain reaction)-based examinations of their mitochondrial DNA. The investigators found a low level of ETC-deficient neurons in the hippocampus, cortex and pontine midbrain. They have established conditions for post-staining single-neuron isolation, and the PCR studies have demonstrated the presence of mutated mitochondrial DNA in groups of isolated neurons. Additionally, a region of the hippocampal formation (the dentate gyrus) has been shown to be ETC-nonfunctional. To overcome certain limitations inherent in traditional PCR, the investigators have recently pioneered the application of a separate technique (rolling-circle amplification [RCA]) to amplify mitochondrial DNA prior to PCR. Using RCA followed by PCR, they will characterize the mitochondrial mutations on a per-neuron basis. (Dr. Bennett can be reached at 434/924-8374; Dr. Miller can be reached at 434/924-9175)

VA Tech Toni Calasanti, Ph.D. (Department of Sociology) "Gender Differences in Informal Care Work for Persons with Alzheimer's Disease"

This study explored the caregiving by husbands and wives of spouses with Alzheimer's disease and related dementias. Data were gathered through interviews with twenty-one caregivers and participant observation in support groups at multiple sites. Findings indicate that husbands and wives perform similar tasks for their spouses, and for similar reasons. However, two caregiving styles were evident. Men tend toward a more instrumental, problem-solving approach that focuses attention on accomplishing tasks, while women's more relational approach focuses attention on the care receivers as life partners. The instrumental approach allows caregivers to engage in emotional distancing; and men's lifelong experiences in mastering tasks and their more dominant positions in society allow them to manage their wives' disruptive and violent behavior, perhaps allowing them to keep their wives in their communities longer. For men, stress results when they become unable to assess problems and act accordingly. At these times, they have fewer personal resources for handling the stress. Women's relational approach, rooted in their caregiving experiences across the lifecourse, eases their gradual transitions into caring for spouses. However, their previous gender-based expectations of themselves lead women to feel more pressure to care for the "whole person," to smooth things over, and to maintain their husbands' happiness and dignity. For women, then, stress occurs when they are unable to keep themselves and their husbands on an even emotional keel and maintain their husbands' autonomy. These findings suggest that, rather than trying to see whether men or women experience the greater stress, research and interventions (such as support groups and educational materials) should focus on gender differences in styles and sources of stress and how to alleviate the latter. (Dr. Calasanti can be reached at 540/231-8961).
VA Tech Shannon E. Jarrott, Ph.D. and P. Diane Relf, Ph.D. (Department of Human Development/Department of Horticulture) "Horticulture Therapy for Persons with Dementia: Replication of a Pilot Study"

Horticulture therapy, which is the use of plant materials and gardening activities adapted to meet individualized needs and treatment goals, has been associated with increased activity, social interaction, concentration, and positive mood among persons with dementia in adult day services. This study compared the responses to horticultural programming of adults with dementia in institutional care settings to those of similar adults in more traditional dementia care programming (games, exercise, crafts), examining the behavioral and affective responses of individuals. Cognitive function scores indicated a moderate level of impairment on average. Both active and passive involvement were higher in the horticultural activities than during the traditional activities, with passive engagement being more common during the horticultural than the traditional activities. In contrast to previous research, exhibited affect in the two conditions was comparable, with interest being the most commonly observed emotion. One possible explanation is the approach and experience of the facilitator, new to the project, who was trained in horticultural therapy but had limited experience working with older adults with dementia. The findings raise questions about the extent to which an intervention depends on the nature and personality of the intervention facilitator and indicate a need to explore the effects of facilitator characteristics on participant experiences. (Dr. Jarrott can be reached at 540/231-5434; Dr. Relf can be reached at 540/231-9279)

ODU Brian K. Payne, Ph.D. and Randy R. Gainey, Ph.D. (Department of Sociology and Criminal Justice) "The Social Context of Providing Care to Alzheimer's Patients: Specifying Interactions Between Social Disorganization, Service Utilization, Burden, and Mistreatment"

Research suggests that individuals with Alzheimer's disease are at a higher risk of mistreatment and experts have attributed this high risk to the stresses that come with providing care to patients with Alzheimer's disease. In this study, the investigators examined whether neighborhood and city-wide factors contributed to caregiver burden potentially influencing mistreatment. Examining 750 case of elder mistreatment from three cities (Virginia Beach, Norfolk, and Chesapeake), they found that Alzheimer’s caregivers and their family members from disadvantaged neighborhoods were less likely than those living in more advantaged neighborhoods to rely on formal services offered by adult protective services. In addition, Alzheimer’s caregivers living in disadvantaged neighborhoods were more likely to experience burden than those living in more advantaged neighborhoods. Burden, as measured by the Virginia Uniform Assessment Instrument, was higher in Norfolk than in the other cities, and most Alzheimer's and dementia cases in Norfolk primarily came from disadvantaged neighborhoods. Using mapping technology, it was determined that support groups were spread evenly across neighborhoods for the most part, but adult day care centers are not as easily accessible in the three cities. (Dr. Payne can be reached at 757/683-3935; Dr. Gainey can be reached at 757/683-4794)

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UVA  Kathleen Fuchs, Ph.D. (Department of Neurology) “Beyond Memory Impairment in MCI: Executive Abilities and Implications for Functioning”

Mild Cognitive Impairment (MCI) is a term used to describe the functioning of elderly adults who demonstrate cognitive deficits that are not severe enough to warrant a diagnosis of dementia. Individuals with MCI have been shown to be at increased risk for developing Alzheimer’s disease (AD). Because memory impairment is a hallmark symptom of AD, studies of MCI have not focused on other brain systems that are critical to the expression of AD, e.g., those involved in executive functioning (abstract reasoning, novel problem solving, ability to recognize and correct mistakes, and ability to think flexibly). In this study, individuals who mainly exhibit a decline in memory functioning (amnestic MCI) were compared with those whose main area of difficulty is in another cognitive domain (nonamnestic MCI) through evaluations of executive functioning, medication management, driving skills, and Magnetic Resonance Spectroscopy (MRS) in specific brain structures implicated in Alzheimer’s disease. There were no statistically significant differences between the two MCI groups on the MRS evaluation. Other results, however, indicate that individuals who carry a clinical diagnosis of MCI exhibit reduced ability in aspects of executive functioning regardless of whether they show prominent memory deficits. Although not impaired, performance was below expectation relative to very high premorbid or baseline functioning on most measures of executive abilities. There was an indication of relatively greater decline on tasks with higher response inhibition and mental flexibility demands than on tasks that primarily tap reasoning and abstraction skills. This decline correlated with performance on a “real world” task of medication management and suggests that individuals with MCI may have greater difficulty with complex activities of daily living than has been supposed. While nearly all subjects in the study had memory complaints, most showed decline in cognitive domains outside of memory functioning, and these declines could have significant implications for an individual’s ability to manage complex tasks independently.

(Dr. Fuchs can be reached at 434/982-4165)

UVA  David S. Geldmacher, M.D. (Department of Neurology) “Eye-Movement Approaches to Information Processing Abnormalities in Mild Cognitive Impairment”

MCI is characterized by measurable difficulties with memory or other thought processes (cognition) that are more severe than expected for age, but which do not interfere with a person’s usual activities. When examining complex visual scenes, individuals with AD have abnormal eye-movement patterns that contribute to their problems in processing visual information. MCI is often a transitional state between healthy aging and AD, and can also be associated with problems in visual processing. This study used a computerized eye-tracking system to compare the eye movements of people with MCI and cognitively healthy adults without significant memory impairment as they scanned visual images of varying complexity. Usable eye-movement data from 19 subjects indicated that although healthy subjects had significantly higher scores on tests of general cognition and memory, the groups did not differ in picture naming ability. Consistent with the hypothesis of the study, individuals with MCI showed significant differences in eye-movement during examination of complicated images that required more intensive information processing. The MCI subjects required more eye movements and had a less efficient search pattern on tasks that require discerning a figure from a complicated background. However, on a simpler object-naming task no differences in eye-movements were observed between groups. The findings suggest that patients with MCI have deficits on tasks requiring complex visual information processing, and have important implications for activities like employment and driving.

(Dr. Geldmacher can be reached at 434/924-5548)
VA Tech    Anne Glass, Ph.D. (Center for Gerontology) “The End-of-Life Care Experience for Alzheimer’s Patients and Their Families”
In today's "death-denying" society, end-of-life care is still a topic often avoided. Therefore, little is known about it, and perhaps least of all about how persons with Alzheimer's and related diseases die. The challenges of providing quality end-of-life care are intensified for this population, given the lack of a predictable trajectory and the communication issues that can arise due to the disorientation of the individuals. Use of hospice is a relatively new development. In this partially-funded pilot project, a qualitative interview instrument was developed to use with four family members after the death of their loved ones. The four cases, two males and two females varying in age from 65 to their 80s, revealed a range of end-of-life experiences, suggesting that there is not just one “good” path. The extent of care needed, the responsiveness of the family member, the health of the caregiver(s), and the housing and support situations can all intersect in a variety of ways that make no one scenario the answer for all. Although most people say they would prefer to die at home, in some situations the nursing home can be a satisfactory choice, particularly if hospice is involved. The project produced a new instrument that can be adapted for future research to address the care needed, as well as a broader definition of the environment and how it supports the end-of-life experience for patients and their families. (Dr. Glass can be reached at 706/425-3222)

Mountain Empire Older Citizens, Inc.    Marilyn Pace Maxwell, M.S.W., and Michael Creedon, D.S.W. “Developing, Implementing, and Evaluating Training Modules for High School Students to Teach Alzheimer’s Caregivers to Use the Internet Effectively as a Tool to Assist in Caring for Their Family Members”
A previous ARDRAF-funded study by Creedon and Maxwell determined that a majority of the Alzheimer’s caregivers surveyed in the Big Stone Gap region would like to be trained on the use of personal computers as a tool to assist them with their caregiving responsibilities; and that these caregivers would welcome instruction about the use of a computer and the Internet from a high school student with specialized training on AD and working with family caregivers. Working in cooperation with Wise County Schools, LENOWISCO Planning District Wired Community Project, and the University of Virginia’s Health Sciences Library Outreach at Wise, the currently-funded investigation recruited 25 senior Caregivers, who wished to use computers and the Internet to help with caregiving duties, and 17 Teen Volunteer trainers from the junior class at Powell Valley High School. The project developed in-depth training for the Teen Volunteers that focused on Understanding Alzheimer’s Care and Helping the Senior Citizen Learner, and five training modules for use by the Volunteer Teens in one-on-one training with Caregivers. With assistance from the region’s Chapter of the Alzheimer’s Association, project staff held three training sessions for Teen Volunteers and then paired them with Caregivers in two combined group training programs. Evaluation results from both the Teen Volunteers and the Caregivers documented the success of the project. Caregivers appreciated the assistance from Teen Volunteers and the skills offered to them. The program lessened Caregivers’ feelings of isolation and lack of confidence in their ability to learn. Teen Volunteers learned a great deal about caregiving and gained a new understanding of the difficulties faced by family caregivers of those with Alzheimer’s disease. They also became more knowledgeable about teaching adult learners and gained insights into their own lives. Recorded observations by the project leaders suggested that the training materials were appropriate for both groups and offered suggestions for future efforts. Eventual statewide replication of the collaboration, Big Stone Gap Teens and Caregivers: Across the Tech Divide, could significantly increase the ability of caregivers to make use of information technology as a caregiving resource. (Ms. Maxwell can be reached at 276/523-4202; Dr. Creedon can be reached at 703/560-7220)
Alzheimer’s and Related Diseases Research Award Fund

FINAL PROJECT REPORTS FROM THE
2005-2006 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.


Alzheimer’s disease is characterized by the presence in the brain of intracellular tangles and extracellular plaques containing the amyloid protein. Attention has recently focused on the role of metals in plaque formation, as amyloid binds to zinc, copper, and iron. Transgenic mouse models of AD have been developed, and brain concentrations of metals can be increased by raising animals with enhanced levels of metal in the drinking water. This study examined how elevated zinc and iron affected memory, amyloid conformation and plaque formation in a transgenic mouse model of Alzheimer’s disease. Transgenic mice raised on enhanced zinc or iron showed deficits in spatial memory, when tested in the Morris water maze, compared to those raised on lab water. Spatial memory is dependent on the hippocampus, where both zinc and iron are found. The mice were also tested on a task designed to investigate their ability to consolidate memories (the Novel Object Recognition task), measuring whether they could remember that they had previously seen an object. Transgenic mice raised on excess zinc showed no preference for the novel object (which normal mice do), performing at chance level. In contrast, Tg mice raised on iron were not impaired on this task, compared to those raised on lab water. Initial analyses of metal content showed that high levels of both iron and zinc were seen in plaques. The beta pleated sheet form of amyloid, the type of amyloid found in the end stage of the disease, co-localized better with the iron than with the zinc. Since zinc has been recommended as a treatment for age related macular degeneration, and ingestion of zinc can deplete copper in the body, the investigator raised some mice with a small amount of copper added to the zinc-enhanced water. This reduced the spatial memory deficits, but did not affect memory for objects. These studies indicate that metals in drinking water can affect memory in a mouse model of Alzheimer’s disease. (Dr. Flinn can be reached at 703/993-4107)

GMU  Pamela M. Greenwood, Ph.D. (Department of Psychology) & Karl Fryxell, Ph.D. (Department of Molecular and Microbiology) “Use of Allelic Association to Study the Genetics of Cognitive Aging”

Although the risk of Alzheimer’s disease is thought to be influenced by several genetic factors, only one gene, APOE, has been conclusively linked to the disease. However, the APOE gene, which is neither necessary nor sufficient for Alzheimer’s disease, also has a broad role in health and repair of neurons in the brain. The investigators hypothesize that genes which affect neuronal health and efficiency of neuronal communication (neurotransmission) may also affect cognitive aging. However, little work has been done to investigate the role of such genes in cognitive aging. Consequently, this research team carried out four experiments on over 400 young and old healthy people to investigate how normal variation in eight genes modulates aspects of attention, memory, and visual search. The genes were selected based on previous work, including their own previous investigations of APOE and neurotransmission genes. Analyses indicate that one neuroprotection gene (BDNF) may modulate attentional function in aging. This indicates that normal variation in neuronal plasticity may play a role in the course of cognitive aging. If confirmed, this finding will provide evidence supporting research into the role of neuronal protection genes as an important avenue for investigating risk factors related to cognitive decline in aging. (Dr. Greenwood can be reached at 703/993-4268; Dr. Fryxell can be reached at 703/993-1069)
College of William and Mary Christine J. Jensen, Ph.D. and colleagues (Center for Public Policy Research) “Promoting an Effective Partnership between Families Coping with Alzheimer’s Disease and Their Healthcare Providers”
The primary objective of this project was to identify the needs of family caregivers and healthcare providers who care for persons with memory loss. A total of 128 caregivers completed a telephone or online survey, and 27 health care providers participated in a focus group and completed a survey. The hypothesis that primary care physicians would be more likely to provide a diagnosis of Alzheimer’s disease than a specialist was not supported. Caregivers reported their primary source of information about the disease was the doctor; however, the majority reported that the doctor provided more information about medications than about the course of the disease or available resources. Physicians and nurses reported that time to spend with patients and families and awareness of community services were their biggest challenges. These findings suggest a number of policy-related recommendations: 1) Increase awareness about the local Alzheimer’s Association among medical professionals and family caregivers; 2) Promote the provision of training programs for family caregivers and health care providers to address the identified health literacy issues and to strengthen the healthcare partnership; 3) Raise awareness of the Certificate for Added Qualifications in Geriatric Medicine (available for physicians board certified in Family Medicine and Internal Medicine) and encourage support for the Geriatric Loan Forgiveness bill; 4) Encourage greater utilization of technology among healthcare providers to track the needs of persons with dementia; and 5) Expand clinical standards to include support for the health care triad in dementia care. (Dr. Jensen can be reached at 757/221-1971)

Virginia Tech Bradley G. Klein, Ph.D. (Department of Biomedical Sciences, College of Veterinary Medicine) and Jeffrey R. Bloomquist, Ph.D. (Department of Entomology) “Modulation of Cognitive Sequelae of Parkinsonism by Environmental Manganese: Implications for Dementia with Lewy Bodies”
The principal aim of this study was to address whether environmental manganese can contribute to, or facilitate, the cognitive decline that has been observed in Parkinson’s disease. Mesocortical and nigrostriatal dopaminergic pathways are respective potential neural substrates for such behavioral deficits, in a mouse model of the Lewy body disorder. The experimental work employed the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model of the Lewy body disorder Parkinson’s disease (PD) and was directed at identifying interactions between Mn and MPTP in behavioral and dopaminergic toxicity. The investigators provided substantial evidence for Mn/MPTP interactions in dopaminergic and behavioral toxicity. They demonstrated that these interactions occur in both motor and cognitive behavior and in respective dopaminergic neural substrates of these classes of behavior (e.g. nigrostriatal and mesocortical pathways). Support was furthermore provided for differential Mn/MPTP interactions in mesocortical vs. nigrostriatal dopaminergic pathways. These results have implications with respect to the underlying mechanisms of cognitive decline in another Lewy body disorder, Dementia with Lewy Bodies, the most common form of neurodegenerative dementia after AD. (Dr. Klein can be reached at 540/231-7398; Dr. Bloomquist can be reached at 540/231-6129)

UVA Michelle King, Ph.D. (Department of Biology) “Direct Interactions between Aβ and Tau in Cultured Cells”
The primary objective of this study was to characterize the relationship between pre-fibrillar β-amyloid and intracellular tau expression, as modeled in a cell culture system. The principal observation used initially was time-lapse photography of tau and tubulin localization following β-amyloid treatment. First, the investigator was able to quantify the microscopy findings by counting cells in populations treated with β-amyloid, and these data provided statistical significance in the initial observation. Second, the findings were confirmed by using an independent biochemical assay for tubulin. And finally, all of the findings were confirmed by microscopy and biochemistry of primary neurons treated with β-amyloid. A significant question regarding the signaling pathway connecting β-amyloid and tau still remains. While the original objectives proposed have been attempted, the research has yet to yield a potential candidate pathway. New experiments are ongoing, as this information is crucial to our understanding of the relationship between tau and β-amyloid and has great potential as a means for designing molecules for therapeutic intervention. (Dr. King can be reached at 434/243-7764)
Two cellular models of Alzheimer’s disease (AD), the transmitochondrial cellular hybrid (cybrid) cell model of sporadic AD (sAD) and the SH-SY5Y cells bearing familial AD (FAD) presenilin1 mutations, overproduce amyloid-beta peptide (Aβ) similar to patients. Aβ requires functional mitochondria to induce cell toxicity, and the survival of neurons in AD is likely regulated by the integration of a complex network of intracellular and extracellular signals. The mitogen-activated protein kinase (MAPK) superfamily comprises the c-Jun NH2-terminal kinase (JNK), p38 MAPK, and the classical MAPK, extracellular signal-regulated kinase (ERK). This study characterized intracellular responses to oxidative stress, beginning with how oxidative stress alters activities of the apoptosis signal-regulating Kinase 1 (ASK-1) or MAPK kinase 4 (MEKK4), and how these upstream “sensors” regulate downstream, pro-apoptotic effector kinases (p38 MAPK, JNK). Cybrids representing sAD were compared to SH-SY5Y cells expressing PS1M146L mutations as a model of FAD and Aβ(1-42) treated control (CTL) cybrids. The investigator found that in all three cell models of AD, Aβ mediated depletion of glutathione (GSH) enhances oxidative stress and seemingly drives the activation of p38MAPK and JNK, in the face of a weak and ineffective ERK and phosphatidinositol 3-kinase stimulated Akt (PI-3K/Akt) activation, resulting in reduced viability. The upstream regulators are distinct with the FAD utilizing ASK-1 as the primary regulator of the cell death, whereas in the cell models of sAD, both ASK-1 and MEKK4 seem to be key regulators of neuronal vulnerability. Activation of the PI3K/Akt signal transduction system by both N-acetylcysteine (NAC) and nerve growth factor (NGF) enhances viability and protects against oxidant injury. Insight gained from these investigations into the signal transduction cascades activated in these cell models provide specific mechanistic insights that will lead to improved approaches to manage the oxidative stress burden in AD brain. (Dr. Onyango can be reached at 434/243-9268)

Weight loss is common in patients with AD, and often occurs before the onset of dementia. Serum levels of leptin, which correlate with levels of adiposity, have been found to fluctuate with weight in both patients with AD and age-matched controls. However, the diurnal fluctuations of leptin, which depend on levels of adrenal glucocorticoids, specifically cortisol, are altered in AD. It has been suggested that uncoupling of leptin and glucocorticoid fluctuations might underlie the weight loss observed in many patients with AD. In mouse models of AD, administration of leptin has been shown to reduce the production of the pathological Aβ fragment of amyloid precursor protein (APP) in the brain. The preliminary experiments in this study addressed the relationship between the adipocyte-derived hormone, leptin and APP. The investigator previously developed a line of transgenic mice (p44), with altered insulin-like growth factor-1 (IGF-1) signaling, that present several hallmarks of AD and undergo accelerated aging, including premature accumulation of ceramide in the brain and reduced serum leptin. Hyperactivation of the IGF-1 receptor in these mice is accompanied by parallel changes in the cascade of events that results in the production of Aβ. This study investigated the hypothesis that the hypothalamic-pituitary-fat cell (HPF) axis that controls metabolic pathways and maintains efficient use of energy, also plays a major role in the pathogenesis of AD. The investigator used microarray analysis to examine age-associated changes in adipocyte-specific gene expression in the p44 mice, and identified the JAK/STAT pathway as a key metabolic pathway altered in mice with accelerated aging and early onset AD-like changes in the brain. This opens up a novel pathway for possible intervention therapy in the treatment of AD and other age-associated disorders affecting brain function. The results provide a global picture of how perturbations in endocrine pathways originating in the periphery, for example, in the adipocyte, can contribute to degeneration of the brain in AD. (Dr. Scrable can be reached at 434/982-1416)
Alzheimer’s and Related Diseases Research Award Fund

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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)
"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.

(Ph.D. Dupree can be reached at 804/828-9536)

"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 ubiquitin-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.

(Ph.D. Macara can be reached at 434/924-1236; Ph.D. Zhang can be reached at 434/982-0083)
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.

*(Dr. Sorrell can be reached at 703/993-1944; Dr. Tompkins can be reached at 703/993-2838)*
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 (ccooogle@vcu.edu).

VCU  Galya R. Abdurakhmanova, M.D., Ph.D. (Department of Pharmacology and Toxicology, School of Medicine) “Novel Epibatidine Analogos as Potential Selective Agonists of α4β2 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 α2-α10 and β2-β4 subunits. The most abundant subtypes of nAChRs in the central nervous system are α4β2 and α7, whereas α3β4 predominates in the periphery. Administration of nAChR agonists with high affinity to the α4β2 nAChR has been proposed as one of the approaches for the treatment of AD. Further, the activation of α7 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 α4β2 versus α3β4 nAChRs, while retaining an agonist effect on α7 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. Abdurakhmanova 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 Aβ 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 Aβ 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., α4β2 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

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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 Paul R. Carlier, Ph.D. (Department of Chemistry) “Hydroxyethylamine Tech 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 Aβ in the brain, by cleavage of the amyloid precursor protein (APP), is thought to be a major mechanism for the disease. Aβ 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 Gianluca De Leo, Ph.D. (School of Medical Lab & Radiation Sciences) Dominion University “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 β3 subunit by BACE1 and γ-secretase modulates sodium channel activity in neurons”

Two enzymes are known to generate the Aβ protein deposits, BACE1 and γ-secretase. In addition to this action on APP, BACE1 and γ-secretase also cleave the sodium channel auxiliary subunits, β1- β4. 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 β3 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 β3 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 Karen A. Roberto, Ph.D., Rosemary Blieszner, Ph.D., and Jyoti Savla, Ph.D. Tech (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 Aβ oligomers as the major toxic species has made Aβ 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 Aβ 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 Aβ 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 Aβ 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 Aβ oligomerization inhibition. Ultimately, the development of these novel chemical tools will help the investigators unravel the role of Aβ oligomers in the pathogenesis of AD. (Dr. Zhang may be contacted at 804/628-8266; Dr. Guo may be contacted at 804/828-6732)
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 2009-2010 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).

Alzheimer's Association  Ellen Phipps, C.T.R.S., and Barbara Braddock, Ph.D.
Central and Western Virginia “Home-based activity intervention program in dementia”  
This study investigated and promoted ‘partnered volunteering’ by pairing University students with individuals who have dementia and their family caregivers to examine an eight-week home-based activity engagement program. The twice weekly intervention provided opportunities for participants to complete activities that were once meaningful in their lives using Montessori-based instruction, therapeutic recreational principles, and environmental modifications. The program was designed to provide an opportunity for successful engagement in life among persons with a diagnosis, to offer respite and support to caregivers, and to foster positive inter-generational relationships. Participants in the intervention group (n = 16) were matched to those with dementia in the comparison group (n = 16) on the basis of sex, age, education, and cognitive screening scores. Comparison group participants selected activities in consultation with the students who implemented the set up, but did not receive regular student visits. Pre- and post-intervention data indicated that activity set up and in-home environmental supports promoted high levels of physical and verbal engagement among participants enrolled in both groups. In contrast to those that did not receive regularly scheduled student visits, caregivers with student support reported statistically significant reductions in burden between program initiation and end. Partnered volunteering may be most beneficial to the caregiver as a supportive intervention to reduce general caregiving stress while sustaining home activity for the individual with dementia.  
(Ms. Phipps may be contacted at 434/ 973-6122; Dr. Braddock may be contacted at 434/924-4000)

UVA  Karen M. Rose, Ph.D., R.N., and Ishan C. Williams, Ph.D.  “Family quality of life in dementia”  
Because a diagnosis of dementia has implications for the overall functioning and well-being of the family unit involved, a reliable and valid instrument to assess the impact of interventions and services provided, or not provided, on family quality of life is needed. The goal of this project was to develop a Family Quality of Life in Dementia (FQOL-D) instrument that can be used in clinical and service settings to measure the impact on families dealing with dementia. An expert consensus panel of 12 representatives from medicine, neuropsychology, nursing, and gerontology completed three Delphi survey rounds to determine the face validity of items. Approximately 40 items were retained, representing five overall domains: family interactions; direct care/activities of daily living support; emotional/behavioral well-being; physical and cognitive well-being; and disease-related support/medical care. In addition, interviews with persons diagnosed as having mild-moderate dementia and their family members were conducted to pilot-test the instrument and collect qualitative data on their individual family quality of life perspectives. The investigators partnered with local Area Agencies on Aging and the Virginia Caregiver Coalition to distribute the FQOL-D across the state. Imminently pending results will confirm the psychometric properties of this clinically-meaningful instrument.  
(Dr. Rose may be contacted at 434/ 924-5627; Dr. Williams may be contacted at 434/924-0480)
VCU  H. Tonie Wright, Ph.D. “Alzheimer’s Aβ amyloid peptide interactions with inflammatory chaperone molecules”

Research suggests that certain aggregated states of the β-amyloid (Aβ) peptide are toxic to brain cells and may also disrupt communication between neurons in the brain. This project hypothesized that the pathophysiological effects of Alzheimer’s Aβ amyloid peptides are modulated by interaction of the peptide with chaperone-like inflammatory molecules in a way that alters the pool of biologically active Aβ oligomer forms. Reciprocal to the effects of Aβ on these molecules, which are also linked to the neuronal damage associated with AD, is the question of how the interacting proteins affect distribution of the different forms of Aβ. Study results showed that the incubation of dissolved Aβ with these proteins changed how the Aβ molecules assembled into aggregates and altered the distribution by resulting in the significant loss of some forms of Aβ. In addition, Aβ peptide and its combination with two of the inflammatory proteins were tested for their effects on brain cells that produce the inflammatory response. Findings show that these proteins diminish the release of neuron-damaging molecules from the activated inflammatory brain cells, and may therefore serve a protective function. Mobilization or stabilization of these proteins, and/or disruption of pathways that lead to immune cell activation, offer possible paths to suppressing brain inflammation and thereby delaying or interdicting the symptoms associated with Alzheimer’s disease. (Dr. Wright may be contacted at 804/828-6139)

UVA  J. Julius Zhu, Ph.D., and Lei Zhang, Ph.D. “Mechanisms for Cdk5-mediated synaptic depression.”

This project investigates the central hypothesis that Cdk5 is a novel rapid homeostatic transmission regulator and aberrant Cdk5 signaling causes the synaptic depression associated with Alzheimer's disease. Preliminary evidence indicated that synaptic activity regulates Cdk5 signaling, which in turns induces a beta-amyloid-independent synaptic depression. The activity-stimulated Cdk5 signaling rapidly depresses transmission independent of transcription and translation, and it depresses NMDA responses prior to AMPA responses, distinguishing itself from beta amyloid (Aβ) and other homeostatic transmission regulators. This suggests that Cdk5 imposes a new type of fast and fine homeostatic regulation on synaptic transmission and dysfunction of Cdk5 signaling is responsible for the early pathogenesis of Alzheimer's disease. Although a number of molecules, including Aβ and a specific Cdk5 activator p25, have been implicated in Alzheimer's disease, it remains unclear which molecule(s) are responsible for the early synaptic pathogenesis. This study has identified p25 as the first molecule responsible for the early pathogenesis of Alzheimer's disease. The results explain the lack of correlation between Aβ deposition and cognitive impairment observed in AD patients and may also account for the failed clinical trials blocking Aβ, which should complementarily stimulate more homeostatic Cdk5 signaling and synaptic depression. The findings suggest additional molecular targets and provide the scientific foundation for developing new detection and treatment strategies for Alzheimer's patients. (Dr. Zhu may be contacted at 434/243-9246; Dr. Zhang may be contacted at 434/243-9562)

2009-2010 ARDRAF Awards Committee

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VCU Severn B. Churn, Ph.D. “Neuronal Mechanisms of Trauma-induced Alzheimer’s Disease”

Several studies have shown an association between traumatic brain injury (TBI) and the development of AD. Recently, similar mechanisms have been associated with TBI-induced memory loss and the development of AD. This investigation focused on the TBI-induced pathological activation of a neuronally-enriched enzyme, calcineurin. Activation of calcineurin has been shown to result in the loss of dendritic spines, the major communication route between neurons. Through several, carefully controlled studies, the investigator was able to demonstrate a prolonged, pathological activation of calcineurin that resulted in delayed loss of dendritic spines. In cortical, but not hippocampal, structures the spine loss could be prevented by the application of calcineurin antagonists acutely after TBI. These studies are the first to identify a cellular mechanism through which TBI could accelerate the progression of AD. (Dr. Churn may be contacted at 804/828-0290)


This study examined whether Tissue Specific Imaging (TSI), a new MRI technique sensitive to the detection of white matter degeneration, and associated T1 quantitative techniques are capable of detecting Alzheimer’s Disease associated changes in middle aged adults, thus potentially serving as a early-detection biomarker for AD. It was anticipated that carriers of the ApoE-e4 genetic risk factor for AD would show a larger degree of white matter degeneration as detected by TSI. While using TSI for differentiating between carriers and non-carriers proved not feasible in the selected cohort, the data acquired is currently serving as the basis for further investigations identifying differences between carriers and non-carriers, and the association of such differences with both cognitive performance and brain anatomical changes. The dataset served as a basis for the development of an automated technique for the detection of Virchow-Robin spaces, a marker of potential vascular pathology that is known to have increased incidence in AD. Furthermore, the investigators are currently exploring the use of texture analysis techniques to develop a more robust methodology for white matter characterization. (Dr. Ikonomidou may be contacted at 703/993-9354; Dr. Greenwood may be contacted at 703/993-4268)

VCU Kate Lapane, PhD “Assessment of Factors which Influence Physician Decision-making Regarding Medication Use in Patients with Dementia at the End of Life”

Few studies have examined the importance of rationalization of medications in patients with advanced dementia nearing the end-of-life, and little is known about the impact of non-clinical factors on prescribing decisions. The investigators evaluated the extent to which nursing home placement, family involvement, and advanced directives influence prescribing decision-making in patients with end-stage dementia. A multidisciplinary team developed four vignettes of patients with end-stage dementia with specific questions relating to discontinuation or initiation of specific medications. Using a modified Dillman approach, the investigator invited a sample of primary care physicians with an active Virginia medical license to participate via email. Of the 269 responders, 191 were eligible for the study. They received vignettes that varied with respect to three randomly assigned factors: 1) Place of residence of the patient (community-dwelling, nursing home); 2) Presence/absence of an advance directive; and 3) Family desires active measures, family desires supportive measures, no family involvement. Chi-square analyses were performed and a balance of potential confounds was achieved through randomization. Continuation of therapies not likely conferring benefits (e.g. statins) was commonplace, regardless of randomly assigned factors. Physicians were less likely to initiate antibiotic therapy for patients with advanced directives (e.g. treating pneumonia with fever: 38% with advanced directives vs. 53% without ($p < .05$). Medication initiation was not influenced by family involvement or nursing home residence. Prescribing decisions for patients with end-stage dementia may be influenced by non-clinical factors. Guidance on strategies to discontinue medications may be warranted. (Dr. Lapane may be contacted at 804/628-2506)
Alzheimer's Association Patricia Lacey, MBA, Sonya Barsness, MSG and Scott Sautter, PhD
Southeastern Virginia “The Impact of Early Alzheimer’s Support and Education Programs on Both Diagnosed Participants and Their Care Partners”

This study investigated the social and psychological impact of EASE (Early Alzheimer’s Support and Education), a program intended to empower diagnosed individuals and their partners to become active participants in their care. The study employed a quasi-experimental (switching replications) research design with validated measures and a wait-listed comparison group. It was hypothesized that, in comparison with those assigned to the delayed intervention group (n = 17), EASE participants (n = 20) would show improvements in personal self-efficacy, mental and physical health status, and the quality of life for those diagnosed with Alzheimer’s disease. No statistically significant group differences were documented between the intervention and wait list groups, but 2 X 2 factorial and repeated measure ANOVAs showed main effects for time of testing on all three outcome measures, and improvements in the intervention group were generally sustained three months after the program. Comparing scores for care partners and those diagnosed revealed statistically significant interaction effects for several of the health status and quality of life indicators. Scores provided by those with the diagnosis decreased (worsened) from the time of pre-testing, while the scores for the care partners increased (improved). However, both care-partners and those with the diagnosis indicated that the overall quality of life for the diagnosed person improved. Given the benefits of the EASE program documented in this study (e.g., lessened depression, improved quality of life, and perceived ability to handle unforeseen situations), it is surprising that the primary hypothesis was not supported. It appears that there was a positive anticipatory effect for the wait-list group in knowing that they would participate. Perhaps simply making the decision to participate in EASE improved their outlook and knowledge of future participation influenced both self-efficacy and quality of life. Although early stage programs have garnered some evidence-based support, additional research is needed to document new models of support and education, and determine the long-term effects of these as the disease progresses.

(Ms. Lacey may be contacted at 757/459-2405; Ms. Barsness may be contacted at 757/773-7841; Dr. Sautter may be contact at 757/498-9585)

EVMS Serina A. Neumann, Ph.D. and colleagues “Donepezil’s Effect on Cardiac Function in Patients with Alzheimer’s Disease Through an In Vivo, Non-Invasive Measure of Peripheral Neuro-cholinergic Function: Relation to Therapeutic Efficacy”

AD is known to affect the nervous system in ways that influence heart function, which may place AD patients at increased risk for cardiovascular-related death. One of the very probable mechanisms of the subtle cardiac autonomic dysfunction in AD is degenerative damage of central nervous structures related to the autonomic nervous system and the influence of these neurodegenerative changes on higher cerebral functions. Involvement of peripheral nervous structures may also play a role. The characterization of changes in cardiac autonomic function in AD patients, however, has been scarcely evaluated. Furthermore, the effectiveness of treatment for AD with standard FDA-approved drugs like donepezil (Aricept®) may be related to the protection of heart function. This investigation measured both cardiac autonomic function (measured by heart rate variability) and mental thinking abilities in four elderly men while taking donepezil for suspected mild AD. The investigators found irregular heart function in two of the four patients; one during the initial evaluation and the other at three months. This study helped to characterize cardiac autonomic function and potential relations to neuropsychological function in AD patients in the early phase of treatment with donepezil, and adds to the understanding of donepezil’s effect on cardiac autonomic function in these patients.
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 2010-2011 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** Malgorzata Dukat, Ph.D. and Galia R. Abdrakhmanova, M.D., Ph.D. “Small Molecules as Negative Allosteric Modulators of α7 nAChRs”

Both agonists and antagonists of α7 nAChRs (i.e., nicotinic acetylcholine receptors) have been shown to be of value in the treatment of AD. Agonists might desensitize the action of ACh at these receptors, thereby reducing cholinergic transmission, and antagonists block ACh transmission. An entirely novel approach is to identify negative allosteric modulators (NAMs) of α7 nAChRs that can selectively, but indirectly, block the effect of ACh at α7 nAChRs without acting at α4β2 receptors. The investigators previously identified one of the first small-molecule NAMs of α7 nAChRs, namely MD-354. Because this compound is a 5-HT3 (serotonin) receptor agonist, the investigators modified its structure to abolish that action, and thereby develop “selective” α7 nAChR allosteric modulators. They synthesized a series of MD-354 analogs and evaluated them in functional assays to determine what structural features are required, and to optimize the pharmacological actions by eliminating affinity for 5-HT3 receptors. The present study delivered proof of concept that small molecules, the guanidines, represent a novel class of α7 nAChR NAMs. Furthermore, the investigators demonstrated that small structural changes to MD-354 diminished or abolished its 5-HT3 receptor affinity, while retaining its α7 nAChR activity. All the NAMs examined display antagonism action at α7 nAChR with half maximal inhibitory concentration (IC50) values ranging from 1.3 – 34.8 µM. To eliminate possible competitive antagonism or channel blocking action, MD-354 and one of the newly synthesized agents were evaluated in voltage-dependence inhibition of ACh experiments and both proved to be α7 nAChR NAMs. In addition, they were assayed for antagonistic activity at α3β4 and α4β2 nAChRs and were found to be inactive, suggesting their selective action at α7 nAChRs. The most potent NAM, was further evaluated in radioligand binding assays for its selectivity among cloned nAChRs (i.e., α2β2, α2β4, α3β2, α4β2, α3β4, α4β2, α4β4) and was found to lack binding affinity at all seven (i.e., Ki > 10,000 nM). This is the first study identifying guanidine analogs as small molecule α7 nAChR NAMs. In contrast to current ACh inhibitors that are limited to symptomatic treatment of cognitive function, these new agents offer the potential for slowing the progression of AD. (Dr. Dukat may be contacted at 804/828-5256; mdukat@vcu.edu and Dr. Abdrakhmanova may be contacted at 804/828-1797; gabdrakhmano@vcu.edu)

**GMU** Jane M. Flinn, Ph.D., Nathalia Peixoto, Ph.D., and Daniel N. Cox, Ph.D. “Behavioral and Inflammatory Changes in a Mouse Model of Late-Onset Alzheimer’s Disease”

The investigators used their mouse model of late onset AD, where the gene APOE4 is important, to examine behavioral and inflammatory changes in mice modeling early onset and late onset AD, together with controls. They examined circadian rhythms, nest building, memory, and the levels of cytokines. Surprisingly the mice carrying the APOE4 gene performed slightly better than the early onset mice, although less well than controls, on measures of circadian rhythms and nest building. (Memory scores were difficult to compare as the controls performed less well than expected.) Their measures of inflammation were also intermediate between those of the controls and the early onset mice. There was a significant correlation between measures of circadian rhythm disruption and inflammation. These were younger mice, suggesting that APOE4 may not be a risk factor at a younger age, and measures of inflammation and circadian rhythm could be useful early indicators of Alzheimer’s disease. (Dr. Flinn may be contacted at 703/993-4107; Dr. Peixoto may be contacted at 703/993-1567; Dr. Cox may be contacted at 703/993-4971)
VCU    Aron H. Lichtman, Ph.D. and Laura E. Wise, Ph.D. “Targeting the Endogenous Cannabinoid System to Treat Alzheimer’s Disease”

In vitro studies have shown that cannabinoid receptor activation can inhibit or reduce the deposition of beta-amyloid plaques and decrease inflammation, critical features of Alzheimer’s disease. While these findings indicate that cannabinoids may be beneficial in attenuating the neuropathology associated with Alzheimer’s disease, very few studies have evaluated if stimulation of the endocannabinoid system can attenuate cognitive deficits and neuropathology in in vivo models of Alzheimer’s disease. The goal of the funded studies was to examine whether elevating endogenous levels of the endocannabinoid anandamide via inhibition of its primary degradative enzyme fatty acid amide hydrolase (FAAH), would have beneficial effects on memory impairments and neuropathological markers in APP/PS1 transgenic mice, an in vivo model of Alzheimer’s disease. The investigators found that repeated administration of the FAAH inhibitor PF-3845 improves memory performance in APP/PS1 transgenic mice, but not control mice, in the Morris water maze. They also found that acute treatment (i.e., drug administration only before water maze testing) with PF-3845 improves memory performance in APP/PS1 transgenic mice, but to a lesser degree than repeated PF-3845 treatment. Immunohistochemistry studies are currently underway to evaluate Aβ plaque formation and the presence of activated microglia in the dorsal hippocampus to determine whether repeated treatment with PF-3845 decreased neuropathological markers associated with Alzheimer’s disease. It is apparent however, that PF-3845 improves memory performance in an in vivo mouse model of Alzheimer’s disease. These findings suggest that FAAH inhibition may have beneficial effects on memory impairments in Alzheimer’s disease. They furthermore provide proof of principle that the endogenous cannabinoid system represents a potential target for medications to treat AD.

(Dr. Lichtman may be contacted at 804/828-8480; Dr. Wise may be contacted at 804/828-7264)

GMU    Robert H. Lipsky, Ph.D. “Functional Characterization of Promoter Polymorphisms of the Human GRIN2B Glutamate Receptor Gene Associated with Altered Memory Functioning in Older Adults”

Mild cognitive impairment (MCI) is a clinical diagnosis that describes a small but measurable decline in an individual’s cognitive abilities, including memory. A person with MCI is at greater risk of developing Alzheimer’s disease. Currently, there are no methods for early detection of MCI or to predict the outcome of MCI or its progression to Alzheimer’s disease. FDA-approved drugs for treating symptoms of Alzheimer’s do not seem to benefit MCI patients, underscoring a need to understand the underlying mechanisms leading to MCI. Using a method that combines an understanding of human genetics and brain imaging, the investigators discovered a variant of the GRIN2B gene, a gene critical for learning and memory that may be a marker for MCI. The funded study determined how this genetic variant controls the GRIN2B gene at the biochemical and cellular level. They found a protein, Elk-1, that binds the DNA of the GRIN2B gene variant, called the A allele. The A allele also activates genes introduced into neuron-like cells maintained in the laboratory. These results support their previous observation that the A allele of the GRIN2B gene is linked to a specific pattern of brain activity seen when older adults (who were otherwise matched for age, gender, and cognitive ability) performed certain memory tasks. Taken together, these results are the first to support the role of a GRIN2B gene variant associated with human memory performance based on molecular and cellular function. They constitute the first genetic association between a functional NR2B gene variant and an endophenotype, a characteristic that is more closely related to pathophysiology of AD than diagnostic markers.

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Alzheimer’s and Related Diseases Research Award Fund

2012-2013 FINAL PROJECT REPORT SUMMARIES

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 2012-2013 round of competition are given below. To receive the full reports, please contact the investigators or the ARDRAF administrator, Dr. Constance Coogle (804/828-1525, ccoogle@vcu.edu).

UVA Inchan Kwon, PhD and Erik Fernandez, PhD
“Revealing the Effect of Food Dyes on Amyloid-Beta Structure-Cytotoxicity Relationships”

Modulation of amyloid-beta (Aβ) peptide aggregation is considered a promising therapeutic strategy to cure Alzheimer’s disease (AD). Although several U.S. Food and Drug Administration (FDA)-approved drugs temporarily reduce symptoms, no treatment exists that slows or stops progression of AD. There is a need to discover more potent molecules and elucidate their relationship to AD pathology. In the search for safe, effective aggregation modulators, the investigators have examined FDA-approved food dyes and their close analogs. They previously reported that erythrosine B (ER) and brilliant blue G (BBG) reduce Aβ neurotoxicity by modulating Aβ aggregation. These exciting results suggest that ER and BBG could be promising lead compounds for AD therapy. For this project, the researchers explored the structural basis for ER and BBG (and their analogs) Aβ binding and the subsequent reduction of cytotoxicity. The preliminary results obtained indicate that a BBG analog, Brilliant Blue R, could be a promising candidate to proceed with in vivo testing in an animal model of AD. In addition, the immunoassays revealed the 10-16 amino acid sequence of the Aβ peptide as a potentially important binding region for aggregation modulators/inhibitors. This work could open the door for structure-based design of molecular or peptide inhibitors that specifically target the 10-16 amino acid sequence of Aβ. Lastly, the immunoassays described in this work provide an economical template for researchers to obtain residue level information without the need for nuclear magnetic resonance spectrometers or other costly apparatus.

(Dr. Kwon may be contacted at 434/243-1822, ikt4@virginia.edu; Dr. Fernandez may be contacted at 434/982-2658, ejf3c@virginia.edu)

UVA Carol Manning, PhD, ABPP-CN, Steven DeKosky, MD, and Ishan C. Williams, PhD
“Vascular Risk Factors and Cognition in African Americans”

Vascular risk factors are associated with dementia. African-Americans have high rates of vascular risk factors and have high rates of dementia. However, dementia and Mild Cognitive Impairment (MCI), often a sign of early dementia, may be under-recognized in African-Americans coming in for general medical appointments. In this study, ninety-six African-Americans who were coming in to see their primary care physicians had cognitive testing immediately. None of the participants were coming to see their doctors because of cognitive complaints. Vascular risks were identified through the participants’ medical records. Vascular risk factors included high blood pressure, diabetes, high cholesterol, history of stroke and cigarette smoking. Cognition was examined in relation to vascular risk factors. Concern about cognitive functioning in participants and physicians was also examined. Data revealed that vascular risks had a negative impact on cognition. According to our cognitive test results, 41% percent of our sample had MCI, despite a lack of cognitive complaints. In addition, neither the patients nor the physicians were aware of the degree of cognitive impairment. African-Americans, coming to see their primary care physicians for reasons other than memory, had high rates of cognitive impairment and vascular risk factors. Vascular risks were correlated with cognitive impairment. These findings indicate high rates of unrecognized cognitive impairment in this population and suggest that patients and physicians may be unaware of these difficulties. Lack of awareness may be secondary to limited appointment time and poor knowledge of risks for cognitive change.

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**Marymount University**  
Julie D. Ries, PhD, PT  
“Balance Training Program Designed for Individuals with Alzheimer’s Disease: The Effect on Balance and Falls”

Individuals with Alzheimer’s disease (IwAD) experience more frequent and more serious falls than their age-matched peers. Balance training is effective in improving balance and decreasing falls in cognitively intact older adults. This study was developed to analyze the effects of a balance training program designed specifically for IwAD, with specific guidelines for communication/interaction and deliberate structure of training sessions. Thirty participants with AD were recruited from three adult day-center programs; twenty-two of them completed at least one post-test session. Balance and mobility tests were administered immediately before and after the three-month program and again three months later. Balance training sessions were 45 minutes, twice per week and were characterized by functional, relevant activities, with considerable repetition, and with sessions consistently formatted with blocks of time dedicated to different tasks. Participants were up on their feet the majority of each session and were individually challenged as much as possible. Although most IwAD did not remember participating in the program week to week, or recognize the researchers after the three-month program, they demonstrated statistically significant improvements in balance. This finding suggests that their bodies had a “motor memory” of the training even if participants did not have a cognitive memory of it. Balance deteriorated after termination of the program, although participants did maintain some improvement three months after the training. Fewer participants experienced falls the six months following program initiation ($n = 5$) than the six months prior to initiation ($n = 9$). This upright and intensive balance training program shows promise for improving balance and potentially decreasing falls in IwAD.

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**VCU**  
Vladimir Sidorov, PhD  
“Identification and Characterization of nAChRs Clustered in Cell Membrane Lipid Rafts Using Novel Patching Technique with Chemically Modified Electrodes”

Neuronal nicotinic acetylcholine receptors (nAChRs) are critical to cell functioning and essential in the development of Alzheimer’s disease. The function of alpha4beta2 and alpha7 subtypes of nAChRs is regulated by association of the receptors with rigid areas of neuronal membranes, known as lipid rafts. The overall goal of this project is to develop a novel technique that allows identification and characterization of the functional properties of nAChRs based on selective patching of the raft and fluid areas of cell membranes with a chemically modified borosilicate electrode. During this initial stage of the investigation, a robust chemical procedure for surface modification of borosilicate electrodes was developed for use in the planned electrophysiological experiments. The procedure allows tethering of a synthetic macromolecule, cyclen 2, which serves as a selective binding agent for the fluorescent dye pyranine. The binding phenomenon is readily observed due to the fluorescence quenching. In order to utilize these electrodes, a series of lipid conjugates with pyranine have been synthesized. The confocal microscopy imaging experiments revealed that the cholesterol-pyranine conjugates rapidly partition into the dynamic areas of cell membranes consistent with the ordered domains (rafts). While being in a rapid lateral motion, the fluorescently labeled cholesterol remained fully accessible for interactions with cyclen 2 attached to the glass surface. Future undertakings will test the hypothesis that the functional behavior of nAChRs is directly affected by their localization in the ordered membrane domains. Such characterization of nAChRs docked in the raft areas of membranes may lead to better understanding of key factors in the development of Alzheimer’s disease as well as to the methods for treatment of this condition.

*(Dr. Sidorov may be contacted at 804/828-7507; vasidorov@vcu.edu)*
Who Forgot the Hippocampus? Potential Involvement in the Neural Circuitry of Attentional Control

The ability to focus on important stimuli and ignore irrelevant stimuli in our environment is essential to the “top down” control of attention. It is suggested that the memory of what is important in an environment is essential to this top-down control, and recent research suggests that attentional impairments may precede or largely contribute to the memory problems associated with dementia of the Alzheimer’s type (DAT). Yet studies examining the brain pathways involved in attention have failed to examine the role of the hippocampus, a brain region commonly associated with memory loss and DAT. The current pilot study tested a rodent model with cholinergic deafferentation of the hippocampus in an operant sustained attention task. Task parameters enabled the introduction of irrelevant distractors in order to assess top down control of attention. Although there was a relatively small sample size ($n = 6$ per group), the data suggest no effect of lesion. However, several parameters (toxin site location, concentration, and task) can be further explored in future research to better understand the potential neural interplay between memory and attention.

Excessive Inflammation in Aging Population Following Brain Injury Impairs Hippocampal Neurogenesis and Cognitive Function: Implication for AD

Recent evidence suggests that impaired neurogenesis in the hippocampus is a critical event and may underlie cognitive deficits in AD. Aging and traumatic brain injury (TBI) are the leading risk factors in the development of AD. This project tested the hypothesis that under neuropathological conditions, aging produces excessive inflammatory responses which impair hippocampal neurogenesis and cognitive function. In Aim 1, serum and brain tissue homogenates from young and aged rats at different time points following TBI were assayed to measure the expression levels of 24 cytokines/chemokines. Another group of animals was used to assess the level of hippocampal neurogenesis. In Aim 2, minocycline and 7,8-DHF were used to target neuroinflammation and neurogenesis for improved cognitive function in animals following TBI. At the early time point, several pro-inflammatory cytokines/chemokines were expressed at high levels in both serum and brain, and the aged animals had a higher expression compared to their younger counterparts. At 3 days post-TBI when the inflammatory mediators were expressed at high levels, a decreased number of newly generated neurons were found in the injured aged brains as compared to age matched sham controls or their younger counterparts. Short term minocycline treatment at the acute stage post-injury significantly attenuated TBI-induced inflammatory cell responses in the brain and the production of several pro-inflammatory cytokines particularly in the aged rats. The administration of 7,8-DHF at the same stage improved cognitive function. These studies suggest that targeting inflammation and neurogenesis may have therapeutic potential to improve cognitive recovery in aging populations.

VCU

Dong Sun, MD, PhD

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(VCU Dr. Sun may be contacted at 804/828-1318; dsun@vcu.edu)
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Assessment of Whether Genetic Risk Factors for Alzheimer's Disease and Vascular Dementia are Associated with Cognitive Impairment in Parkinson Disease
Cognitive impairment is a common and disabling feature of Parkinson disease (PD). This study sought to identify genetic risk factors for cognitive impairment in PD to provide insight into disease pathophysiology, improve prognostication, and inform personalized treatment strategies. Because Alzheimer’s disease (AD) pathology and cerebrovascular pathology are present in Parkinson disease patients with earlier cognitive impairment, we focused on studying genetic risk factors for AD and vascular dementia in PD. This study took advantage of two large existing PD datasets with single nucleotide polymorphism arrays and mini-mental state exam (MMSE) scores. The investigators performed quality control procedures on genetic data and problematic data were removed prior to analysis. Candidate genetic markers for 9 genes associated with AD and two genetic markers linked to vascular dementia were selected for analysis. We then analyzed the association between the available genetic markers and MMSE scores in the two datasets. There were no associations between any of the genetic markers and lower cognitive scores in either PD population. However, there was an association between one of the genetic risk factors for AD (PICALM SNP rs3851179) and greater cognitive impairment in PD subjects > 70 years old. This finding is consistent with pathological data showing that AD pathology is a greater contributor to dementia in PD patients with older onset. Based on our findings, future studies should consider the interaction of age and genetic risk factors for AD in the development of cognitive impairment in Parkinson disease. (The investigators may be contacted: Dr. Barrett, 434/243-2012, mjbarrett@virginia.edu; Dr. Worrall, 434/924.2783, bbw9r@virginia.edu; Dr. Turner, 434/982-4208, sdt5z@virginia.edu)

ODU Christianne Fowler DNP, RN, GNP-BC and colleagues
The Impact of an Interdisciplinary Virtual Healthcare Neighborhood on Sleep, Healthcare/Social Support, and Self-Efficacy among Caregivers of Elderly Persons with Dementia
This study was conducted after development of a website called the Virtual Healthcare Neighborhood (VHN). Investigators included an interprofessional group of healthcare providers. Participants were caregivers (CG’s) of individuals with AD or a related dementia. The care recipients (CR) were all unable to leave the home without the assistance of another person and the CGs all had a computer with internet access. Twenty-eight CGs were enrolled. The control group (n = 14) received usual care plus an actigraphy band to monitor sleep quality and quantity, while the experimental group (n = 14) received support and education via the VHN website as well as the actigraphy band. Over a four month period, weekly educational topics and a social support blog site were delivered via the website. Several measures were taken for both groups before and after the study period. Measures included insomnia severity, CR’s ADL needs, social support, general self efficacy and CR agitation/aggression. All participants were also interviewed at the conclusion of the study and qualitative data was obtained regarding the use of the VHN, actigraphy band and their overall caregiving experience. Preliminary data analyses show improvements on social support measures in the experimental group after the VHN intervention. The qualitative data thus far reveal themes showing that CGs found value in the weekly information material and the blog site. There were several CGs from both groups that had difficulty setting the actigraphy band at bedtime, resulting in some missing data. (Dr. Fowler may be contacted at 757/683-6869, cfowler@odu.edu)
CCAL    Karen Love, B.S., Elia Femia, Ph.D., and Sonya Barsness, M.S.G.
Promoting Change and Action in Person-Centered Care Practices Using a Multi-Media Approach

Person-centered care is the gold standard for the care of people living with dementia. However, missing is the understanding of what person-centered care is, how it is delivered, and most importantly, why it makes a difference in a person’s life. To address this challenge, a video, “Person-Centered Matters,” was produced to evaluate its effect on promoting awareness and understanding of person-centered care and the benefits. In total, 218 dementia care professionals were recruited to view either the “treatment (person-centered dementia care)” video or a “control (treatment-as-usual)” video about dementia care. In addition, 99 care professionals, family care partners, and people living with dementia participated in one of six focus groups to provide further feedback. Those who watched the treatment video experienced a change in their understanding of person-centered care and felt greater competence to implement its practices. That effect was sustained at a 1-month follow-up. The video helped participants think differently about people with dementia, understand the importance of person-centered care, and inspired them to be successful in implementing it. Participants who watched the treatment video were also more likely than those in the control condition to respond emotionally to the video. Treatment participants were more likely to indicate that the video made them feel good about their work, describing it as inspirational or motivational. Finally, treatment group participants were more likely to want to better know people with dementia, focus on their strengths, and allow them to express their preferences. (The investigators may be contacted: Ms. Love, 703/533-322, karenlove4@verizon.net; Dr. Femia, 703/532-5133, Elia.Femia@verizon.net; Ms. Barsness, 757/773-7841, Sonya@sbcgerontology.com)

Liberty    Gary D. Isaacs, Ph.D.
University Remodeling of DNA Methylation Associated with Increased Beta Amyloid Deposition in Mice

Although several mutations have been associated with patients suffering from Alzheimer’s disease (AD), several lines of evidence suggest that AD development might be caused by chemical modifications of the base DNA sequence (e.g., cytosine methylation, cytosine hydroxymethylation). The aim of this project was to identify regions of the genome that become epigenetically altered as cells progress toward an AD-like state. To this end, the investigator and his team utilized DNA microarrays to map the locations of both cytosine methylation and cytosine hydroxymethylation in an AD mouse model system. Mice expressing two AD-related transgenes comprised the AD-like condition group while mice lacking the transgenes served as the AD control group. The transgene positive mice produce more beta amyloid plaques than control mice, they do significantly worse on cognitive function experiments, and die at a younger age. This study identified 223 genes with a significant increase in DNA methylation and 330 promoters with a decrease in methylation in the AD condition. For the hydroxymethylation (HMe) analysis, 243 genes with increased HMe levels and 187 genes with decreased HMe levels were found. Surprisingly, there was very little overlap between the genes that change methylation and HMe levels (approximately 2%) suggesting that the HMe changes are not the result of methylation changes, but might represent their own distinct epigenetic input. In addition, the investigation also implicated a novel set of microRNA genes in the pathology of AD. This approach to identifying AD-related epigenetic changes on a genomic scale represents a novel application of current technology, and these findings provide more evidence as to the role of DNA modifications in AD development. (Dr. Isaacs may be contacted at 434/582-2224, gdisaacs@ liberty.edu)
Radford Lisa L. Onega, Ph.D., R.N.
University Bright Light Therapy for Individuals with Dementia
Many older adults with dementia living in long-term care facilities experience depression and agitation, which cause angst and personal suffering. Prior to this research, evidence was inconclusive but indicated that bright light exposure may reduce depression and agitation in long-term care residents with dementia. The purpose of this study was to determine if the degree of improvement in depression and agitation scores over the course of eight weeks was significantly greater in persons with dementia receiving bright light exposure than in persons with dementia receiving placebo light exposure. Forty-seven individuals participated in the study, with 23 in the bright light group and 24 in the low level light group. Results revealed that 30 minutes of bright light exposure twice every weekday for eight weeks was associated with significant improvement in levels of depression and agitation in comparison to changes observed in a low intensity light exposure control condition. Participants randomly assigned to the bright light condition showed statistically significant improvement in eight of nine measures of depression and four of four measures of agitation. This effect was large in magnitude and would clearly be noticeable in everyday life. For participants in the control group, significant improvement was observed for only one of the nine measures of depression and for none of the four measures of agitation. These findings support the use of bright light therapy for older adults with dementia to decrease depression and agitation and thereby improve their quality of life. (Dr. Onega may be contacted at 540/831-7647, lonega@radford.edu)

GMU Maren Strenziok, Ph.D. and Pamela Greenwood, Ph.D.
The Impact of Auditory Perception Training on Brain Activation and Connectivity in Attention Networks, Reasoning Ability, and Everyday Cognitive Function in Patients with Mild Cognitive Impairment
Cognitive stimulation is a promising approach aimed at preserving cognitive function and independence in daily life. New evidence suggests that cognitive training transfers to non-trained everyday problem solving. This is important insofar as heightened problem solving may help maintain independence in everyday life and slow conversion from Mild Cognitive Impairment (MCI) to AD. This study hypothesized that cognitive training increases parieto-temporo-occipital cortex-dependent attentional control demands in MCI patients. The investigators found preliminary evidence that episodic memory and everyday problem solving improved following training. This is important as episodic memory decline is a hallmark of AD and improved everyday cognitive functions may slow conversion to AD. In the healthy control subjects, there was preliminary evidence that training altered visual information processing in the superior temporal cortex (STC) involved in auditory and visual processing. That auditory perception training altered STC activation measured with a visual attention neuroimaging task is important in revealing the transfer of sensory training in one modality (auditory) to functional changes in another modality (visual). This suggests new hypotheses about mechanisms of training-related cognitive change that may explain improvement in visual tasks such as those used to assess everyday problem solving. The investigative team plans to continue their assessment of possible links between changes in sensory-attention networks, memory, and everyday cognitive functioning. (Dr. Strenziok may be contacted at 301/318-8912, mstrenzi@gmu.edu; Dr. Greenwood may be contacted at 703/993-4268, pgreenwl@gmu.edu)
Multiple pathogenic factors have been suggested to contribute to the etiology of AD. The multifactorial nature of AD could be exploited therapeutically to design novel multifunctional ligands that tackle various risk factors simultaneously as an innovative strategy, thus increasing the success of disease-modifying agent development. The investigators have been developing hybrids of curcumin and melatonin, two natural products that possess multifunctional properties, and have been extensively studied in AD disease models, as potential neuroprotective agents for neurodegenerative diseases. Conceptually, the hybrid strategy incorporates structural features that are essential to the biological activities of different drug structures into one single molecule. It is hypothesized that the curcumin/melatonin hybrid will improve the multifunctional properties by self-synergy within one molecule that may not be achievable by a traditional combination of these two compounds that may miss the ideal timing window. One lead compound, K30, was identified for further optimization. Importantly, K30 has been demonstrated to show anti-inflammatory and metal-chelating properties, thus confirming the multifunctional nature of this compound. In the proposal, we proposed to 1) evaluate K30 in a transgenic AD mouse model to confirm and validate the in vivo effects of K30 on Aβ pathology; 2) develop new analogs of K30 through structural optimizations employing chemical design, organic synthesis, and various cell-based tests. Overall, we have achieved our goals and the following has been accomplished: 1) Twenty two compounds have been successfully synthesized and structurally characterized; 2) Cell based assays of these compounds identified one lead compound with nanomolar potency of neuroprotections; 3) In vivo characterization in intact mice demonstrated that this lead compound can cross the blood brain barrier efficiently and is orally available; 4) In vivo studies in transgenic APP/PS1 mice demonstrated that the lead compound significantly reduced Aβ pathology after three months treatment. (Dr. Zhang may be contacted at 804/628-8266, szhang2@vcu.edu; Dr. Lee may be contacted at 216/368-6887, hyoung-gon.lee@case.edu)
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 2014-2015 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).

GMU Robin Couch, PhD

Neuroprotection and Alzheimer's Disease

Nerve growth factor (NGF), a protein naturally produced in the brain, is capable of preventing neuronal cell death, such as that associated with Alzheimer’s disease (AD). Recent preclinical and clinical AD studies have noted a reduction in the rate of cognitive decline upon treatment with NGF. However, because NGF is unable to penetrate the blood brain barrier, current means of delivering NGF directly to the brain are highly invasive and cost prohibitive. Oral drugs capable of stimulating the upregulation of NGF in the brain are preferred. To that end, this research group has identified protein kinase C (PKC) and several of its downstream effectors as critical to the upregulation of NGF protein. They used a series of protein specific agonists and antagonists to validate select members of the PKC signal transduction pathway, thereby highlighting them as promising targets for the development of new therapeutics for the treatment of AD. (Dr. Couch may be contacted at 703/993-4770, rcouch@gmu.edu)

UVA Erin Pennock Foff, MD, PhD and Benjamin Purow, MD

Investigating the Role of miR-762 in Mediating Disease in C9ORF72-Based Frontotemporal Degeneration

It is known that amyotrophic lateral sclerosis and frontotemporal dementia can be caused by a common genetic mutation in the C9ORF72 gene. The investigators discovered that a particular regulatory microRNA had high predicted affinity to bind this mutation, and questioned whether inappropriate binding of that molecule could contribute to disease process. In this funded project, they were able to demonstrate that: a) the predicted microRNA shows altered activity in blood and stem cells derived from patients with the disease, b) specific genes are misregulated in the cells in a manner consistent with microRNA disruption, and c) those disruptions may be contributing to some of the known features of the disease, including excitotoxicity to glutamate. These results constitute the most critical first steps in validating the investigators' proposed mechanism's potential role in mediating part of the disease phenotype. This initial data has also contributed to a new initiative in the lab to build more sophisticated model systems using three-dimensional stem cell cultures that will better approximate normal brain structure and cellular interactions. (Dr. Foff may be contacted at 434/243-1006, epf4b@virginia.edu; Dr. Purow may be contacted at 434/982-4415, bwp5g@virginia.edu)

Warren Jonathan Winter, MD and J. William Kerns, MD

Memorial Pharmacologic and Non-Pharmacologic Management of Behavioral and Psychological Symptoms of Dementia (BPSD): A Mixed-Method Pilot

Because atypical antipsychotic medications (APs) for treating the behavioral and psychological symptoms of dementia (BPSD) can cause rare severe side effects (SE), an FDA Black Box Warning (BBW) was issued to reduce their use. This mixed methods study explored why roughly 20 percent of Virginia nursing home patients still remain on APs. Quantitatively, they trended the prescribing rates of all psychotropics in Virginia’s Medicaid dementia population since the FDA BBW. Not only has AP utilization not decreased, but use of alternative medications for BPSD that have not been shown to be safer or more efficacious are increasing. Qualitatively, they assessed the experiences and perceptions of POAs and nurses (caregivers) about decision-making processes concerning pharmacologic/non-pharmacologic approaches to BPSD management. Caregivers feel that non-pharmacologic strategies (NPS) can work for most BPSD, but have limits. Community POAs also feel “on their own,” in developing and utilizing NPS, with little help from physicians and inadequate supporting resources. Furthermore, caregivers see pharmacologic strategies as effective, especially if the ‘right’ medication is used in addition to NPS. What’s more, no caregiver reported ever knowingly observing the severe SE of APs described by the BBW. These severe SE of APs were rarely discussed by physicians and poorly understood by caregivers. (The investigators may be contacted at 540/631-3700, jwinter@valleyhealthlink.com, bkerns@valleyhealthlink.com)
GMU    Joseph J. Pancrazio, PhD  
**Analysis of Amyloid Beta Effects with Living Neuronal Networks**
Assays based on dishes of cells offer a means of screening potential therapeutics and accelerating the drug development process. In this study, the investigator used dishes of interconnected brain cells or neurons on electrical recording devices called microelectrode arrays to examine the effects of amyloid-β 1-42 (Aβ42), a biomolecule implicated in the Alzheimer’s disease process. The research showed that a special form of Aβ, oligomeric but not the monomeric, diminishes electrical activity from the network of neurons on the microelectrode arrays. This observation is important because clinical and animal model results suggest that the neuroactive form of Aβ is the oligomer and so the assay method is sensitive to the pathologically relevant form of the molecule. The effects of the oligomer are persistent over a period of at least 24 hours and do not appear to be associated with cell death. In addition, the researcher demonstrated that the excitatory receptors in the brain, that are triggered by the neurotransmitter glutamate, play a role in the effects of Aβ42 on neuronal network activity. Exposure to blockers of these receptors modulated the time course of Aβ42 oligomer effects on the neuronal networks. Pretreatment of the neuronal networks with two model therapeutics, methylene blue and memantine, reversed the effects of oligomeric Aβ42. These findings suggest that cultured neuronal networks may be a useful platform in screening potential therapeutics for Aβ induced changes in neurological function.
*(Dr. Pancrazio may be contacted at 703/993-1605, jpancraz@gmu.edu)*

Virginia    Doris T. Zallen, PhD, Golde Holtzman, PhD, and Kye Kim, MD  
**Tech**  
**Evaluation of a Web-Based Decision Aid for People Considering a Genetic Testing for Alzheimer’s Risk**
This team of investigators developed an online decision-aid prototype as an educational tool to help in making decisions about whether or not to use the APOE genetic test to estimate genetic risk for Alzheimer’s disease. This prototype was evaluated by over 1,200 participants in a two-part (before and after) survey-based study. Both the quantitative data (the responses to the survey questions) and qualitative data (additional written comments from the participants) reveal a high level of satisfaction with the tool as a means of providing information relevant to this decision. Using feedback obtained in response to a request for suggested improvements to the tool, the prototype was re-designed to provide a greater ease of functionality and greater accessibility on a wide variety of platforms. In addition to validating the usefulness of this tool for individual decision-making, this study identified areas which may be the subject of future consideration by the medical community and by government agencies. These areas include: a) ways of encouraging the further creation of online tools as educational aids in making genetic-testing and other health-care decisions, and b) the consideration of policies to help ensure that consumers have adequate information as they consider genetic testing for Alzheimer’s disease and other disorders. The enhanced decision aid will now be made available online at no cost to the wider public.
*(Dr. Zallen may be contacted at 540/231-4216, dzallen@vt.edu; Dr. Holtzman may be contacted at 540/239-2949, holtzman@vt.edu; Dr.Kim may be contacted at 540/981-8025, kykim@carilionclinic.org)*

UVA    Zhiyi Zuo, PhD  
**Environmental Enrichment Reduces Postoperative Cognitive Dysfunction**
Postoperative cognitive dysfunction (POCD) often occurs in patients 60 years of age or older. It not only affects daily living, but also is associated with increased death after surgery. Recent studies indicate that inflammation in the brain, an abnormal process for many chronic brain diseases including Alzheimer’s disease, may be involved in POCD. This investigation employed environmental enrichment (EE) to test whether that non-pharmacological intervention could reduce POCD in aged mice. The results showed that EE reduced surgery-induced learning and memory impairment. The reduced brain cell generation needed for learning and memory was also attenuated after surgery. These results provide initial evidence to suggest that improved environment after surgery may be a potential way to reduce POCD. These data should help in the design of clinical studies to test the beneficial effects of EE in humans.
*(Dr. Zuo may be contacted at 434/924-2283, zz3c@virginia.edu)*
Alzheimer’s and Related Diseases Research Award Fund

2015-2016 FINAL PROJECT REPORT SUMMARIES

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. The awards this year were enhanced by a $25,000 donation from Mrs. Russell Sullivan of Fredericksburg, in memory of her husband who died of dementia. Sullivan awards are indicated by an asterisk (*). Summaries of the final project reports submitted by investigators funded during the 2015-2016 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).

EVMS  Frank J. Castora, PhD and Randolph Coleman, PhD

*Biochemical Systems Theory Modeling of Alzheimer’s Disease Using Mitochondrial Genes Involved in Amyloid Precursor Protein and Tau Processing*

Mitochondrial dysfunction is a critical component in the pathogenesis of Alzheimer’s Disease (AD) where deficits in oxidative capacity and energy production have been reported. The investigators previously found abnormal expression of several genes critical to mitochondrial energy production in AD brains. In this study, total RNA was isolated from age-matched controls, AD and AD+ (AD possessing a mitochondrial DNA mutation) frozen autopsy brain samples, and the abnormal expression of 168 genes involved in mitochondrial function and energy production was assessed. A subset of mitochondrial genes was found to be critically involved in mitochondrial energy production and function in AD brains. The investigators have now begun to build a mathematical model of AD using Biochemical System Theory (BST). Through the development and application of appropriate differential equations, the flux of various metabolites and small molecules will be simulated and used to generate a testable model of mitochondrial involvement in AD pathogenesis. *(Dr. Castora may be contacted at 757/446-5657, castorff@evms.edu; Dr. Coleman may be contacted at 757/221-2679, racole@wm.edu)*

UVA  Alev Erisir, MD, PhD*

*Ultrastructural Neuropathology in Transgenic Models of Alzheimer’s Disease*

This investigation aimed to reveal brain alterations that are too small or too subtle to be detected by the microscopic tools used for studying lesions in AD. Using transgenic mice aged between 3 and 12 months that overexpress amyloid and electron microscopy (EM), the earliest alterations in brain structure were characterized prior to the onset of cognitive decline. The brain regions known to display AD pathology were surveyed to characterize the emergence and severity of ultrastructural lesions therein. In addition, immuno-EM was used to identify when and where Aβ-associated neuronal deterioration started. Their systematic analyses revealed evidence of a previously unappreciated culprit for the cognitive decline that emerges before 5 months of age. Particularly, the oligodendrocytes, the cells that make myelin, become hypermotile in the presence of overexpressed amyloid. The consequence is over-myelination, or rather disruptive myelination, all across the brain. Basal forebrain and entorhinal cortex, the sites of first neurodegeneration in human AD, contained oligodendrocyte hypermotility-related pathologies at the youngest ages. Other regions displayed progressively more severe pathologies at later ages, in a spatial pattern similar to the consensus staging protocol for the neuropathologic assessment of human AD established by the National Institute on Aging and the Alzheimer’s Association. By the ages when cell death is prominent, myelin outfolds gave rise to massive bulb structures, which are transitional to neuritic plaques. These results provide insights into the mechanism and role of oligodendrocyte hypermotility that will guide future studies of AD neuropathology in the human brain. *(Dr. Erisir may be contacted at 434/243-3549, ae4h@virginia.edu)*
Investigating the Relationship between Benzodiazepine Medications and the Development of Blood Brain Barrier Dysfunction as Risk Factors for Alzheimer's Disease

The main focus of this project was to accumulate experimental evidence that would establish a mechanism of the observed association between benzodiazepine use and the development of AD. The goal of these studies was to investigate the effects of benzodiazepine medications on the integrity and function of the blood brain barrier (BBB). Utilizing the in vitro human BBB model already established in the investigator’s lab, studies confirmed the hypothesis that select benzodiazepines alter measurements of barrier integrity. The ability of the barrier to maintain its selectivity was only modestly affected by the benzodiazepines, and treatment with alprazolam did not result in changes in amyloid β flux across the barrier. Further work will be conducted to examine the effects of the benzodiazepines on the expression of the transport proteins involved in amyloid beta passage across the BBB. (Dr. McRae may be contacted at 804/628-5076, nmpmcrae@vcu.edu; Dr. Slattum may be contacted at 804/828-6355, pwslatm@vcu.edu)

Controlling Neuronal Sphingosine-1-Phosphate as Alzheimer’s Disease Therapy

Sphingosine-1-phosphate has been shown to be a potent lipid signaling molecule that protects neurons from dying as a result of biological insults. Six synthetic small molecules designed to specifically inhibit the activity of one or both of the sphingosine kinases (SphK1 & SphK2) were tested on hippocampal neurons cultured under conditions that mimic the stress environment in brain regions affected by AD. Three compounds showed promise for preventing pathophysiological changes in hippocampal neurons and thus promoting their long-term survival in culture. In addition, neurons treated with one of these contained more synaptic-like structures, indicating that inhibiting these kinases either promotes the formation of new synapses or stabilizes and prevents the loss of already existing synapses. The investigators are currently determining the optimal dose for the designed compound, and testing the therapeutic benefit on cortical neurons. The data obtained should serve as the basis for developing treatments for AD. (Dr. Santos may be contacted at 540/231-5742, santosw@vt.edu; Dr. Valdez may be contacted at 540/526-2076, gvaldez1@vtc.vt.edu)

Individuals with Dementia at Adult Day Health Care Centers: Examining the Effects of Individualized Music on Mood and Agitation

The Music and Memory Program© is an international program that brings personalized music selections into the lives of people with dementia. A mixed method, six-week quasi-experimental two-group design was implemented to examine the effects of linking individualized treatment goals to strategic music implementation on behavioral and emotional functioning in a sample of older adults with dementia participating in five different adult day health care centers. The results demonstrated a positive change in mood and a decrease in agitation for the intervention group participants based on behavioral observations. This research will increase understanding of a non-pharmacological, situation-specific individualized music intervention that can be used by formal and informal caregivers to impact the behavior of individuals with AD. (Dr. Tompkins may be contacted at 703/993-2838, ctompkin@gmu.edu)
Molecular Mechanisms of Amylin as a Novel Contributor to Alzheimer’s Disease

Epidemiological studies have shown a link between type 2 diabetes (T2D) and the risk for AD. A feature common to both diseases is the formation of amyloid peptide aggregates. The peptide associated with AD is amyloid beta (Aβ), and for T2D, it is amylin. Amylin can possibly travel to the brain, and aggregate themselves into amylin amyloids, or combine with Aβ, to form amylin/Aβ-crossed amyloids. This project applied an interdisciplinary approach involving cellular, biochemical, biophysical, and computational methods to define the amylin amyloid species, establish cell-based neurotoxicity assays, and assess amylin/Aβ-crossed amyloid formation and toxicity. The investigators were able to define three amylin amyloid species that have distinct sizes and shapes. They further defined how amylin forms amyloid and fibril using multiple biochemical and biophysical methods. They established cell-based functional assays that can be used to assess amylin-induced neurotoxicity. Two compounds used in Alternative and Complementary Medicine to treat diabetes, inflammation and neuroprotection were found to potently inhibit amylin-induced neurotoxicity. Mechanistic insights were provided through detailed and comprehensive cellular, biochemical, and computational simulation studies. These results serve as the basis for a future comprehensive research program to elucidate molecular events that contribute to AD as well as to devise potential treatment strategies. (Dr. Xu may be contacted at 540/231-1449, binxu@vt.edu; Dr. Bevan may be contacted at 540/231-5040, drbevan@vt.edu; Dr. Wu may be contacted at 540/231-8442, wul3@vt.edu)

The Neurophysiology of Driving Impairments in Early Alzheimer’s Disease

Getting lost in familiar surroundings, wandering, and unsafe driving are some of the most debilitating early symptoms of AD and represent a major safety concern. These visual-spatial impairments have been associated with a decreased capacity to perceive optic flow, the pattern of visual-motion that is naturally observed during common tasks like ambulation or vehicular driving. Using an electroencephalographic technique known as event related potentials (ERPs), the investigators recorded specific brainwaves that are generated by optic flow and found significant differences between AD patients and controls. In this study they combined ERPs with a virtual reality driving test to explore the links between decreased brain responsiveness and driving capacity in a group of 19 patients with early stage AD and 18 cognitively normal elderly controls. Only one patient passed the driving test and only one control subject failed it. A comparison of test scores showed highly significant differences between the two groups, supporting the utility of virtual reality in the assessment of driving capacity. The researchers also found statistically significant differences in the magnitude of ERPs, with AD subjects showing smaller responses that were also linked to poor driving scores and impaired cognitive tests. These results have several implications; the differences in response magnitude between groups and their association to cognitive scores support the potential utility of ERPs as early markers of Alzheimer’s. Furthermore, the association between ERPs and driving score supports the notion that impaired perception of optic flow is partly responsible for impaired driving capacity and suggests that ERPs may serve as screening tools. Future studies with larger samples will be necessary to generalize these findings and establish normal parameters. Longitudinal studies will also explore the use of optic flow ERPs as markers of disease progression. (Dr. Fernandez-Romero may be contacted at 434/ 243-5611, rf6u@virginia.edu)