Alzheimer's and Related Diseases Research Award Fund

2013-2014 FINAL PROJECT REPORT SUMMARIES

The Alzheimer's and Related Diseases Research Award Fund (ARDRAF) was established by the Virginia General Assembly in 1982 t 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 2013-2014 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).

UVA **Matthew J. Barrett, M.D., M.Sc., Bradford B. Worrall, M.D., M.Sc., and Stephen D. Turner, Ph.D.**

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. Turnerst, 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 University **Gary D. Isaacs, Ph.D.**

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 (eg., 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 University **Lisa L. Onega, Ph.D., R.N.**

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, pgreenw1@gmu.edu)***

VCU **Shijun Zhang, Ph.D. and Hyoung-gon Lee, Ph.D.**

Development of Curcumin/Melatonin Hybrids as Neuroprotective Agents for Alzheimer's Disease

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) valuate 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)***