
Alzheimer's and Related Diseases Research Award Fund

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**FINAL PROJECT REPORTS FROM THE
2001-2002 ALZHEIMER'S RESEARCH AWARD FUND**

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 structures 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 A β ₁₋₄₂ 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 A β ₁₋₄₂-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-3 β (GSK-3 β) and MAP kinases (JNK, p 38, and ERK) signaling pathways. Lithium, used to treat bipolar disorder, was found to protect against A β -induced neurotoxicity and tau phosphorylation by mechanisms that may involve anti-apoptotic as well as GSK-3 β regulation activities. The investigators made significant progress in understanding pathways by which the important Alzheimer's peptide, A β , causes injury to neurons, and have pointed the way to possible treatments. (*Drs. Savory and Ghribi may be contacted at 434/924-5682*)

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**VCU/MCV Jurgen Venitz, M.D., Ph.D. and Yuxin Men, M.D. (Department of Pharmaceutics)
"Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling of the Interaction of IV Scopolamine and Physostigmine in Healthy Elderly Volunteers"**

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)*

VCU/MCV Janet H. Watts, Ph.D., O.T.R. and Jodi L. Teitelman, Ph.D. (Department of Occupational Therapy)

"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)*