Studies in Dementia and Neurodegenerative Diseases

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Principal Investigators

KAPOGIANNIS, DIMITRIOS

Institution

National Institute on Aging

Contact information of lead PI
Country

USA

Title of project or programme

Studies in Dementia and Neurodegenerative Diseases

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 649,715.60

Start date of award
Total duration of award in years

8

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Intramural... Clinical Trials and Supportive Activities... Dementia... Diagnostic Radiology... Neurodegenerative... Neurosciences... Prevention... Translational Research

Research Abstract
Predictors and biomarkers of Alzheimer’s Disease (AD) In collaboration with Dr. Ed Goetzl from

UCSF and other investigators, we developed a methodology for isolating blood exosomes and enriching them for neuronal origin by immunoprecipitation using neuronal surface markers NCAM and L1 CAM. To date, we have conducted five case control studies measuring exosomal Ab, tau, Ser and Tyr phosphorylated IRS-1, and other proteins, in AD and control subjects. We found highly significant differences that, for some proteins, accurately discriminate between the two groups. In addition, exosomal differences may be present at the preclinical stage and may predict AD. I published five manuscript on the topic (in the journals Alzheimer's and Dementia, FASEB J (twice), Neurology, and Annals of Clinical and Translational Neurology). One major goal for the coming year is to validate exosomal markers as diagnostic and prognostic biomarkers of AD in large cohorts from the Baltimore Longitudinal Study of Aging (BLSA), the Alzheimer's Disease Neuroimaging Initiative (ADNI), The Harvard Aging Brain Study, and the WRAP (Wisconsin). The BLSA, Harvard Aging Brain Study, and WRAP are ideal to assess longitudinal changes in these markers and their potential to predict AD at the preclinical stage, disease progression and conversion from MCI to AD. In collaboration with the NIA 3T MRI Facility manager, Dr. David Reiter, I have employed a novel Magnetic Resonance Spectroscopy (MRS) methodology at the NIA 3T MRI facility, which allows us to obtain in vivo measures on brain metabolites (glucose, lactate) and neurotransmitters (glutamate and GABA), which are relevant to AD pathogenesis. First, I conducted a study of healthy volunteers combining MRS with resting fMRI, which provides measures of brain functional connectivity, and showed a link between neurotransmitter levels and brain connectivity. The study was pubmished in Neuroimage. In a case-control study of patients with MCI/AD and healthy volunteers, we show higher glucose and lactate, and lower glutamate and GABA in patients compared to controls, suggesting that these MRS markers may be used as diagnostic biomarkers for AD. The manuscript is currently under preparation. I also studied the association between cognitive performance and clinical status in AD and CSF inflammatory markers and found that higher levels of one particular pro-inflammatory cytokine, IL-12, predicts better cognition and less brain atrophy; this manuscript is currently under review. In collaboration with Dr. Mohamad El Haj from University of Lille, France, we conducted three studies on autobiographical generation of past and future events in a cohort of AD patients compared to controls. We found that future and past events are more similar in patients compared to controls and that the ability to generate future events is closely related with the patient's episodic memory. In addition, the ability to generate future events was associated with Frontal Lobe functions. These findings suggest that remembering the past and imagining the future rely on common brain structures, which are both impaired in AD. We published two studies describing these findings in the journals Neuropsychologia, Hippocampus, and Journal of Alzheimer's disease. In addition, we published two systematic review on Episodic Memory in aging and AD, and on the effects on APOE in the journal Aging Research Reviews. Treatment studies in AD I conduct a proof of concept Phase II, double blind, randomized, placebo-controlled, clinical trial to assess the safety and tolerability of exendin-4 (exenatide) treatment in participants with Mild Cognitive Impairment (MCI)/early AD. To this date, 57 participants have been enrolled and started on treatment with study drug (exenatide or placebo). Participants receive study drug for 18 months and outcome measures are being collected every six months. Sixteen participants completed the study, six participants withdrew from the study, and six continue participation. My goal for the new year is to reach the enrollment target of forty participants. I also continue to conduct a Phase I, double-blind, placebo-controlled, ascending, single-dose, safety, tolerability and pharmacokinetic study of Bisnorcymserine, a selective butyrylcholinesterase inhibitor, in healthy volunteers. Inhibition of butyrylcholinesterase is a novel therapeutic approach for symptomatic treatment in

moderate/advanced AD. Finally, this year we acquired final IRB approval for a study of Intermittent caloric restriction (ICR)implementing 5-2 CR (alternating 5 days of regular calorie intake and 2 days of CR). This is a 8-week study of 5-2 CR in overweight middle aged subjects to assess potential beneficial effects on insulin resistance, metabolism, cognitive performance, fMRI activity and biomarkers. If this study is positive, ICR may be a candidate intervention for primary prevention of AD at midlife.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A