JOSEPH & KATHLEEN BRYAN
Alzheimer's Disease Research Center

Request for Proposals

To be selected for inclusion in a NIA Program Project Grant Submission

Letter of Intent due: November 4, 2016

The Joseph and Kathleen Bryan Alzheimer's Disease Research Center (Bryan ADRC) in the Department of Neurology invites the submission of investigator-initiated projects for inclusion in a Program Project Grant (P01) submission. The applications should address the scientific theme, the Role of APOE in Normal Brain Aging and Alzheimer's disease.

The two main risk factors for the development of Alzheimer's disease (AD) are age and ApoE genotype. Common variants of the APOE gene are strongly associated with the risk of developing Alzheimer's disease and shift onset to a younger age, but the gene's role in the disease and its interaction with aging have been unclear. The gene codes for a pleiotropic protein (ApoE) which regulates multiple metabolic and signaling pathways in the periphery and in the Central Nervous System, and, in addition, is a ligand for a number of receptors. Individuals, who carry the ε4 isoform, show some imaging biomarker changes as well as subtle cognitive disorders in advance of symptomatic disease. Further, the ε2 isoform has been implicated as a protective variant associated with exceptional longevity in several clinical series and population cohorts. At the cellular level, structural differences in the ApoE isoforms determine functional variations that affect brain immunity, vascular disease, and neuronal functions. Minor differences in the isoforms give rise to variability in domain interactions with multiple molecules and in turn influence the activity of ApoE in an allele-specific manner in both healthy and pathological states. And emerging evidence also suggests that the interplay between genetic and epigenetic variations could be one of the molecular mechanisms behind ApoE's association with multiple physiological conditions and diseases.

The purpose of this RFA is to bring together different disciplines at Duke and UNC –CH to examine the biology of APOE with an emphasis on its role in normal brain aging and in Alzheimer's disease (AD). A major hypothesis under discussion is whether APOE acts to accelerate physiological processes involved in normal brain aging.

Areas of research interest include, but ***are not limited*** to following areas (builds on NIA RFA PAR-15-357):

1) Define neural, genetic, molecular and metabolic profiles of APOE in conjunction with behavioral profiles that distinguish normal brain aging from pathological aging.

2) Employ a lifespan approach to study APOE during vulnerable periods/physiological transition states to better understand the mechanisms of its risk and protective effects.

3) Characterize the impact of APOE on age-related changes in glial cells (astrocytes, microglia, and oligodendrocytes) and other non-neuronal cells and in relationship to AD pathogenesis.

4) Identify neural cell populations, brain regions, neural circuits and/or large scale networks (connectome) that are vulnerable in brain aging and explore how APOE influences these circuits, leading to the development of AD.

5) Characterize in a systematic, integrative way how APOE impacts aging processes in brain (e.g. genomic instability, epigenetic changes, senescence, mitochondrial/energy dysfunction, etc.).

6) Define the APOE and age-related aberrant or compensatory neural activities in epileptogenic, sensory, motor, emotional or cognitive systems and their relationship to development of AD.

7) Characterize the molecular, cellular, synaptic and neural circuitry mechanisms underlying brain plasticity, e.g. neurogenesis or adaptive cell stress response pathways, in aging and the influence of APOE.

8) Elucidate molecular, cellular, and physiological changes in the brain glymphatic and lymphatic transport systems during aging in relation to APOE genotype and its contribution to the development of AD.

9) Integrate research aimed at understanding the (epi) genetics, molecular and cellular networks, neural connectivity, and complex biology of brain resilience in context of differing APOE isoforms and in exceptional longevity

10) Develop integrative research to understand how aging in peripheral systems (e.g. immune, endocrine, metabolic, microbiome) interact with the CNS to impact brain aging and the initiation and progression of AD neurodegenerative changes.

11) Develop and employ novel animal models, such as rodents, canines and non-human primates, which spontaneously develop neuropathological signs of AD at older ages. These studies could include animal models, human or animal in vitro cultured cells including iPSCs, gene-edited cells and in vivo humanized APOE animal models.

12) Examine the effects of specific pathways on age-related risk of AD and the interaction with ApoE isoforms with these pathways.

13) Complete molecular profiling (genomic, proteomic, lipidomic, metabolomic) studies of stored human biospecimens or specimens collected as part of other clinical studies to understand the relationships of APOE genotypes, mRNA, protein levels, cellular functional pathways and pharmacogenetics effects that may be affected differentially by APOE genotypes and the relationships of these factors for age-related risk of AD. Integrative, multidimensional analysis of diverse sources of data is a strong approach for this area of research.

14) Develop studies of the pharmacogenetic interventions for AD prevention.

15) Examine the interaction of key biological variables including sex and ethnicity on APOE-specific age-related risk of AD.

16) In vitro or animal model studies on the effects of small molecules that might act as structural modifiers that modulate ApoE effects, influence epigenetic or other regulation of ApoE expression or function or influence pathways differentially affected by APOE genotype.

Applicants should submit a one page description of their project- specific aims to: Bryan ADRC RFA committee attn.: Roberta Demery at roberta.demery@duke.edu by October 24th. The ADRC executive committee will contact all applicants to discuss inclusion of their project in planned NIH grant submissions.