2021 CART Grant Recipients

Dr. Susan Kaech, *Salk Institute for Biological Studies, La Jolla, CA*

$300,000 Roger Ackerman Memorial Grant

CART Research Goal – **Infectious history as a determinant of age-related inflammation in Alzheimer's disease**

We hypothesize that the infection-induced functional reprogramming of brain-resident microglia and TRM cells serves as a double-edged sword that on one side provides long-term immunity to specific pathogens locally in the CNS, but on the other side predisposes the CNS to increased risk of inflammation, tissue stress and neurodegeneration. Here, we will test the hypothesis that successive viral infections, naturally experienced over one's lifetime, progressively increases the numbers of 'inflammatory trained' TRM cells and microglia in the brain that hasten age-related inflammation and predisposition to AD.

Dr. Jose Abisambra PhD, *McKnight Brain Institute, University of Florida, Gainesville, FL*

$200,000 Grant

CART Research Goal: **Test the central hypothesis that tau impairs ribosomes in Alzheimer's disease thereby damaging memory.**

We propose that tau impairs memory in these diseases by interfering with ribosomes. In this application, we propose to use highly innovative and sophisticated omics- and imaging-based approaches to: Aim 1: Test the hypothesis that tau-associated ribosomes translate distinct transcripts into new proteins. This aim will determine how much damage tau inflicts on translation of RNA into new proteins. We will perform Ribosome Profiling with RNA-Seq footprinting coupled with quantitative proteomics in Alzheimer's disease brains compared to nondemented controls acquired from our 1Florida ADRC Biorepository and Biospecimen Bank. This aim will identify selectively translated mRNAs and new proteins that are impacted by toxic tau.

Dr. Nicholas Barthemely, *Washington University School of Medicine, St Louis, MO*

$200,000 Grant

CART Research Goal – **To create a Blood Test to screen for early-stage Alzheimer's Disease in an asymptomatic population.**

We hypothesize that plasma Aβ42/40 ratio becomes rapidly abnormal together with the emergence of brain amyloid plaques at early preclinical stage. Then, plasma Aβ42/40 ratio remains constant at preclinical and symptomatic stages. In parallel, plasma ptau181 and ptau217 levels constantly increase before symptomatic phase and could be used to predict the risk of conversion to symptoms during the asymptomatic A B Figure 2. A Plasma Aβ42/40 ratio measured by MS is significantly decreased in amyloid PET participants (Panel A) and can be used to predict amyloid positivity with good accuracy (Panel B). Adapted from Schindler et al. 2019.phase. Thus, plasma ptau biomarkers could be use 1) to reinforce the confidence in identifying amyloid positive status as determined using plasma Aβ; 2) to estimate the stage of the disease in asymptomatic individuals within AD continuum. We predict the high accuracy and specificity of MS assays would detect subtle changes in plasma Aβ42/40 ratio and ptau217 providing better performance over immunoassays in detecting early brain pathology due to AD. We will design a MS assay measuring plasma Aβ and tau isoforms then assess assay accuracy in detecting amyloid positive participants in different cohorts including late onset and autosomal dominant AD.

Dr. Ma-Li Wong, *SUNY Upstate University of Medicine, Syracuse, NY*

$100,000 Grant

CART Research Goal – **Investigating the novel functional role of an essential splicing factor, CWC22 (pre-mRNA-splicing factor CWC22 homolog), in alternative splicing of genes that may contribute to AD pathology and cognitive deficits.**

This proposal represents a highly innovative research line focused on the role of alternative mRNA (messenger RNA) splicing in the cognitive decline of Alzheimer's disease (AD) and aging. We propose to investigate a potential mechanism underlying AD- and age-associated splicing changes meditated by upstream regulatory splicing factors, such as CWC22 (pre-mRNA-splicing factor CWC22 homolog). Alternative mRNA splicing is a fundamental gene regulatory process that allows multiple protein isoforms from a single gene. Existing data suggest that abnormal RNA splicing in the aging brain may play a role in AD. Differential exon usage in the amyloid-beta precursor protein (APP) gene was found in the aging hippocampus.

Dr. Gilbert Gallardo, *Washington University School of Medicine, St Louis, MO*

Grant - $100,000

CART Research Goal –**Identifying anti-inflammatory molecules for therapeutic intervention of Alzheimer's disease.**

In the proposed studies, we aim to identify new pharmacological inhibitors of the α2-NKA that display CNS penetration in collaboration with the Washington University Center for Drug Discovery (CDD). The CDD provides small-molecular libraries that will be screened with a high-throughput Na/K ATPase Microplate assay and a cell culture model of AD. Our studies also highlight the importance of understanding the mechanism by which astrocytes display neurotoxicity. We have identified the mTOR and autophagy signaling cascade as potential contributors for regulating astrocytic-dependent neurotoxicity in additional preliminary data. To better understand the mTor-autophagy signaling, we propose an in-depth investigation in cell culture models and mouse models of tauopathy. This knowledge may identify new molecular targets for therapeutic intervention of AD.

Dr. Se Hoon Choi, Massachusetts Hospital, Harvard Medical School, Charlestown, MA

Grant - $100,000

CART Research Goal – **Impact of exercise-hormone irisin on tauopathy**

Although much effort has been made to develop drugs that reduce tauopathy, most of them have been discontinued because of toxicity and/or lack of efficacy. Thus, it is crucial to explore options based on lifestyle factors known to ward off tau pathologies. Exercise, particularly, has shown to reduce tauopathy. Irisin is a myokine stimulated by exercise. We recently collected preliminary data showing that irisin reduces pTau levels in a three-dimensional human neural cell culture model of AD (3D-AD cultures). Based on this data, we hypothesize that irisin has neuroprotective effects, by reducing tauopathy, in AD models in vitro and in vivo. The objective for this proposal is to rigorously test this hypothesis by integrating 3D-AD cultures and tau transgenic P301S mice using mechanistic molecular and biochemical techniques, morphological studies, and behavioral testing.