

## PILOT AWARDS – FISCAL YEAR 2018

### Institute on Aging Pilots

#### 1. Biomarkers for misfolded a-syn fibril strains in Parkinson disease

PI: Rizwan S. Akhtar, MD, PhD

**Abstract:** Parkinson disease (PD) is a progressive neurodegenerative disorder that affects the elderly and causes significant motor and cognitive problems. PD occurs when the protein a-synuclein (a-syn) misfolds and aggregates to form toxic amyloid fibril structures that lead to the death of neurons. Recent information suggests that the conformation of these protein fibrils change over the course of the disease. Over time, new a-syn fibril conformations might be even more detrimental for the patient. Misfolding and aggregating of a-syn likely starts long before PD is diagnosed, but we do not have a method to detect this process and do not know when it first occurs. This knowledge would greatly improve the clinical care of PD patients by helping to make an earlier diagnosis and by providing a dynamic, disease-relevant biomarker of the disease process.

Many efforts have been made to measure a-syn directly in biological fluid samples from PD patients. However, these efforts have met with little practical success in the clinic, owing mostly to the fact that traditional measures of a-syn have not focused specifically on the pathological forms of this protein. One particular challenge has been to design assays that can distinguish natively folded a-syn from its misfolded forms.

In this project, we propose to use two new antibodies made at Penn to develop a novel assay to measure misfolded a-syn amyloid aggregates in the blood and CSF from PD patients. We will make synthetic a-syn aggregates to help develop this assay. We will test this new assay using a cohort of PD patients that have been very well characterized clinically, and who have blood and CSF samples already collected. We will make comparisons between their clinical features and the levels of misfolded a-syn that is measured, to test the hypothesis that specific misfolded a-syn fibrils correlate with advanced symptoms of the disease. These efforts will generate a new biomarker focused on a-syn fibrils. We expect that this new biomarker will help us understand what causes PD and how to predict complications in PD.

#### 2. Elucidation of Cell-type Specific Transcriptomic Profiles in Neurodegenerative Brain

PI: Mingyao Li, PhD

**Abstract:** Alzheimer's disease (AD), the most common cause of dementia, affects 5.2 million Americans and 35 million worldwide. Genome-wide association studies (GWAS) have identified susceptibility loci from AD patients that suggest multiple biological pathways contributing to its genetic architecture. However, most GWAS-identified variants are located in non-coding regions suggesting that dysregulation of RNA expression may determine AD susceptibility. Transcriptomics provides a promising avenue to assess GWAS regions that show altered gene expression. While many transcriptional changes in AD are likely due to dysfunctional cellular pathways, changes in the cellular composition of affected brain regions are also likely to impact gene expression levels, but dissection of the two confounding effects has been technically challenging. To gain a better understanding of the transcriptional changes in AD, we propose to characterize gene expression variations in single-cell RNA-seq data from human brains. Using cell type-specific gene expression from single-cell RNA-seq data as a reference, we will infer cell type-specific gene expression and alternative splicing in bulk RNA-seq data from AD and normal brains, and compare their cell type composition and cell type-specific gene expression and splicing profiles. Findings from this project will allow us to examine cell type-specific effect in AD.

#### 3. Endotypical Correlations of Speech Patterns in Frontotemporal Degeneration

PI: Mark Liberman, PhD

**Abstract:** In this study, we propose to implement automated methods of speech analysis developed at Penn Linguistic Data Consortium (LDC) [1] for analyzing digitized speech samples in a large cohort of patients with Frontotemporal

Degeneration (FTD) collected at the Penn FTD Center. We hypothesize that prosodic markers in the speech of FTD patients will be reliably detected, quantified and monitored with the use of an automated approach in the early stages of disease: bvFTD patients [2], for example, may show an abnormal pitch range and variability; non-fluent/agrammatic PPA (naPPA) may be identified by their high pause rate, reduced speech rate as well as speech errors, measured through the variable lengthening, shortening, omission and distortion of phonemes [3]; in semantic variant PPA (svPPA) there may be reduced production of concrete nouns [4] that may modify or distort prosody. Since phonetic changes and dysprosodies may be very subtle yet measurable even at the early stages of disease, we also hypothesize that they will be measurable in the speech patterns of asymptomatic mutation carriers of FTD related disorders. We also propose longitudinal studies of speech: speech pattern changes over time, and we expect these changes to be detected and serve as a quantitative marker of progression and an endpoint in treatment trials. Thus, we will be studying subtle acoustic and linguistic features in cross-sectional and longitudinal speech samples from symptomatic cases as well as asymptomatic mutation carriers prior to the manifestation of any other clinical features. We will associate these acoustic features with specific pathologies (FTLD-tau, FTLD-TDP, and AD) identified in autopsy cases and individuals with a pathogenic mutation that causes a specific form of pathology, and relate autopsy-confirmed patterns to speech patterns in living sporadic cases with biomarkers in CSF [5], single nucleotide polymorphisms (SNPs) [6], as well as anatomic regions on MRI [6] that provide converging evidence consistent with a specific pathology [7].

#### **4. Characterization of Alzheimer's disease-linked MHC Polymorphisms within the HLA-DRB Locus**

**PI:** Dimitri Monos, PhD and Brad Johnson, MD, PhD

**Abstract:** Two recent, large and independent GWAS meta-analysis studies report that two intergenic SNPs, rs9271192 and rs2516049 in the class II region of the major histocompatibility complex (MHC), located centromeric to HLA-DRB5 gene, are associated with Alzheimer's disease (AD). These SNPs are located within a ~40Kbp linkage disequilibrium block ( $R^2 \geq 0.8$  within the CEU population) containing the HLA-DRB5 gene, which is found in approximately 15% of MHC haplotypes. Additionally regarding gene expression HLA-DRA transcript was significantly altered in AD brains as compared to control brains. Recent research from our group demonstrates that both the DRA and DRB5 genes encode additional genomic elements, including novel microRNAs, encoded within intron 5 of the HLA-DRB5 and intron 1 of DRA gene. Preliminary data suggests that these particular miRNAs is computationally predicted to target transcripts of genes that have been associated with AD pathogenesis through GWAS studies, including eQTL loci that have been associated with AD. Importantly, because of the complexity of the MHC locus, it has, until recently, been difficult to obtain full and accurate sequence information for MHC haplotypes. It is therefore likely that there are additional and as-yet uncharacterized sequence variations in linkage disequilibrium to the two SNPs that may explain the increased risk for AD. Identifying such variations should yield clues to which factors encoded within the region might contribute to pathogenesis. Our approach will involve the capture and sequencing by next generation sequencing (NGS) of the HLA-DR region, a 153kbp genomic fragment, including all the relevant DRA and DRB genes, using a NGS-based methodology developed in the Monos lab and shown to provide credible sequencing data of high coverage (92-97%) and accuracy (99.99%) for the whole MHC (4 Mbp). For this pilot study we will work with a limited number of subjects (40 to 1) demonstrate that our NGS approach can successfully characterize the region and 2) identify novel sequence variants that will provide candidates for future studies to explain how this region of the MHC contributes to AD pathogenesis.

## Penn Alzheimer's Disease Core Center (ADCC) Pilots

### 5. Palliative Care Consultations for Persons with Advanced Dementia in the Medicare Skilled Nursing Setting

PI: Mary Ersek, PhD

**Abstract:** Palliative care is a patient and family-centered approach to care that is recommended for persons with advanced dementia (PWAD). Key components of this approach are: 1) open discussion of the course of illness; 2) establishment and communication of patient- and family- directed goals that guide health care; 3) aggressive prevention, early identification and treatment of illness-related symptoms; and 4) identification of psycho-spiritual needs and approaches to mitigating suffering. Unfortunately, many PWAD, especially those who are cared for in nursing homes, lack access to palliative care. This is particularly concerning in post-acute (i.e., following hospitalization) nursing home care, where PWAD are likely to receive intensive physical rehabilitation services and treatments such as feeding tubes that are burdensome rather than beneficial for the person's well-being. Our project's goal is to refine and test a palliative care consultation intervention for PWADs who are receiving post-acute care in nursing homes. Our long-term goal is to shift the current models of dementia care in nursing homes to a person-centered model that results in better symptom control, enhanced communication, and enhanced quality of life for PWAD and their families.

### 6. Effects of episodic memory on economic decision-making in older adults with and without biological markers of preclinical Alzheimer's disease

PI: Joseph Kable, PhD

**Abstract:** Older adults often struggle with financial decision-making, and they are disproportionately exploited for financial gain. The consequences of this decline in decision-making capacity can be devastating, placing undue burdens on relatives and public entitlement programs. Decision-making difficulties in old age may stem primarily from difficulty in learning and acquiring values for later decisions. In particular, learning values from single experiences requires a functioning episodic memory system, a learning system that deteriorates rapidly as individuals age. It is unknown how well older adults can use episodic memories of single events to make adaptive decisions. Moreover, learning has never been investigated in older adults in the social domain, where appropriate learning about others is fundamental for avoiding financial fraud. Here we propose to test if older adults can learn to associate stimuli with rewards after one experience in order to make adaptive economic decisions, in both the social and non-social domain. We will also investigate the effects of preclinical Alzheimer's disease (AD) and medial temporal lobe structural alterations, which are also related to episodic memory decline (but are usually unaccounted for in aging studies) on episodic memory-based decision-making. For this pilot study, we will recruit participants from the well-characterized cohort of older adults at the ADCC, many of whom have already undergone MRI and PET imaging to test for biological markers of AD. This pilot is the PI's first foray into studying decision-making in health aging, as his research program to date has focused exclusively on the cognitive and neural bases of decision-making in young adults. We have consulted Dr. David Wolk, co-director of the Penn Memory Center and Clinical Core Leader and Associate Director of the ADCC, and he supports this research as proposed. He will facilitate recruitment from and access to data from the ADCC cohort. This pilot study will serve as the basis for a joint NIH R01 application with Dr. Wolk, investigating the effects of multiple forms of memory on adaptive decision-making.