

PILOT AWARDS – FISCAL YEAR 2017

Institute on Aging Pilots

1. Exploring functional and structural neuroimaging biomarkers of Huntington's disease progression

PI: Pedro Gonzalez-Alegre, MD, PhD

Abstract: Huntington's disease (HD) is an inherited neurological disease characterized by the progressive malfunction and death of neurons in different parts of the brain, preferentially in an area known as the basal ganglia. Patients afflicted by HD develop progressive dementia, psychiatric disease, and a movement disorder characterized by chorea (dance-like involuntary movements) and impairment of voluntary movements. Death ensues about 20 years after onset. No treatment is known to alter the disease course. HD is in an excellent position to be the first age-related neurodegenerative disease for which a treatment that slows down the disease course is developed. The reason for this is that, through a simple genetic test, we can identify who will develop the disease decades before onset. Different therapeutic approaches from multiple laboratories, including gene silencing strategies or stem cell infusions, among others, are currently in the preclinical IND-enabling stages that need to be completed before moving onto early phase clinical trials in HD patients. For those, it is critical to have reliable biomarkers of disease progression that can be used not only to detect the efficacy of the treatment tested, but also its potential toxicity. Some simple MRI-based measures are currently used with this goal, mostly measuring the progressive loss of volume of a component of the basal ganglia known as the putamen. Here, we propose to merge the significant strengths of the Penn Neuroimaging Center and the new Penn HD Center to explore novel imaging measurements of brain structure and function in HD patients at different stages of the disease and normal controls. Some of these novel imaging modalities have been developed at Penn and never applied to the HD brain before. In addition, the image acquisition strategy we will use will be harmonized with the NIH-funded Human Connectome Project, which provides access to control data from a very large sample of healthy subjects (N=1500). The data generated will help the investigators in the selection of clinical endpoints for a future HD trial. Furthermore, the investigators will use this preliminary data to seek NIH funding from the Human Connectome Project, which is now extending to "Connectomes Relate to Human Disease".

2. Multiplexed fluorescent microscopy for quantification of tau-mediated neurodegeneration

PI: David Irwin, MD, MSTR

Abstract: There is a large variability in the range of clinical symptoms associated with Alzheimer's disease neuropathology and other tauopathies; however, detailed comparative neuropathological studies that examine heterogeneity in the regional distribution of tau-mediated neurodegenerative changes in the brain that underlie these clinical symptoms have not been systematically studied. A major limitation to such studies is that traditional neuropathological assessments are based on subjective ordinal scores (i.e. mild, moderate, and severe) which lack the sensitivity and variance of a continuous measure of disease burden needed for data-driven patient classification statistics. In cancer research, multiplexed methods of immunofluorescence in human tissue microarrays, which consist of multiple small core biopsies of different patient tumor specimens, are used to quantify the reactivity of multiple cell markers and protein targets simultaneously. These efforts have led to high-throughput means to obtain deep phenotypic information of tumor tissues to guide treatment decisions. These methods have not been previously studied in neurodegenerative disease brain tissue. Here, we propose to first validate a method for constructing a human brain tissue microarray for use with a novel multiplexed immunofluorescence platform which will simultaneously quantify 10 markers related to tauopathies. We will use these novel methods in our pilot cohort of well annotated autopsy samples to develop a high-dimensional dataset of regional pathological burden in over 200 cases and use data-driven cluster analysis to define neuropathological subtypes of Alzheimer's disease and other tauopathies. This project will be the first study using multiplexed immunofluorescence technology in neurodegenerative disease and will help address an important gap in knowledge on the heterogeneity of distribution of tau-mediated neurodegeneration that will guide future treatments for these disorders. We will build on these data in a future R01 proposal to examine the genetic influence on the selective regional vulnerability in the brain which define neuropathological subtypes of tauopathies.

3. Mitochondrial NAD, redox state and aging biomarkers

PI: Lin Li, PhD

Abstract: It is of great research interests to identify aging biomarkers and to prevent and delay aging and aging-associated diseases. The dysfunction of mitochondria, the power plants for cellular energy production, is regarded as a hallmark of aging; but whether and how mitochondrial metabolism affects the aging process remains unclear. The concentration of NAD (NAD^+/NADH , NOT same as oxidative stress) are key factors regulating cell metabolism and signaling; their roles in aging process are still unresolved due to the limitations of the whole-cell or whole-tissue based measurements that have been applied to date. In this study, we propose utilizing our unique expertise in mitochondrial redox imaging to investigate whether total NAD and redox state within the mitochondrial compartment change during aging and how they may affect the aging process. The synergy between and complementary expertise of the labs of the PI and CoPI will enable probing of the mitochondrial NAD and redox state via a combination of biochemical/biological assays and fluorescence imaging methods. In Aim 1, we will survey the mitochondrial NAD and redox state changes in various mouse organs (brain, liver, heart, muscles, etc.) at young, middle, and old ages. We will also identify potential imaging biomarkers for aging based on analysis of redox imaging heterogeneity. In Aim 2, we will study primary mouse neurons in culture as a more tractable model system to test the roles of mitochondrial NAD and redox state in the health and survival of cells. The award of this pilot grant will enable the PI, a senior investigator holding two R01s, to shift his research from cancer to aging using metabolic imaging methods, and eventually develop an extramurally-fundable project.

4. Genetic risk factors associated with coincident Alzheimer and Parkinson Disease in neuropathologically confirmed cases

PI: Adam Naj, PhD and Jon Toledo, MD

Abstract: Alzheimer (AD) and Parkinson's disease (PD) are the most common causes of dementia and movement disorders. These neurodegenerative diseases are commonly present together in the same subjects; approximately one third of demented subjects with AD show significant Lewy body (LB) pathology, with most subjects presenting a lower LB burden. Conversely, one third of PD dementia subjects have a diagnosis of coincident AD pathology. In addition, these two pathologies interact with each other. PD cases with coincident AD pathology present a higher burden of LB, whereas in AD cases two different LB distribution patterns are observed, one of which is not observed in PD. Genome-wide association studies (GWAS) have mainly relied on clinically diagnosed cases without biomarker or neuropathological confirmation of diagnosis, and some associations observed in GWAS of AD may be capturing undiagnosed LB pathology. In addition, most neuropathologic studies to date have focused on presence or absence of pathologies, but have not explored different pathology distribution patterns as observed in AD cases with coincident LB.

We propose to study genetic associations in two samples, the National Alzheimer's Coordinating Center (NACC) cohort (3,418 autopsied GWAS cases) with available neuropathological diagnosis and Center for Neurodegenerative Disease Research (CNDR) cases with detailed topographic neuropathological evaluation (560 cases). In these samples, we will 1) perform a discovery GWAS to identify new associations of genomic variants with AD and PD pathology (CNDR and NACC samples) and associations with specific LB deposition patterns in AD cases (CNDR sample) and 2) evaluate if genetic variants identified in prior AD genetic studies are associated with coincident LB pathology and its deposition pattern. Cognitive and neuroimaging biomarker correlates will be explored in the Alzheimer's Disease Neuroimaging Initiative (ADNI, including 1,700 subjects).

Penn Alzheimer's Disease Core Center (ADCC) Pilots

5. Family matters: How does Alzheimer's Disease genetic testing impact relationships?

PI: Angela Bradbury, MD

Abstract: Progress in discovering Alzheimer's disease (AD) genes and biomarkers has led to clinical trials in order to discover treatments for persons who are cognitively normal but at risk of developing AD dementia. One of these prevention trials is the Alzheimer's Prevention Initiative's (API) Generation Study (NCT02565511). This recently launched multi-site, 8 year-long clinical trial is enrolling cognitively normal persons who are at heightened genetic risk of developing AD in order to test whether a drug can slow the emergence of cognitive decline. The goal of this proposed IOA pilot study is to leverage the Generation study to discover why people chose to either share or not share their genetic risk of AD with family, healthcare workers, employers, and others. The more we understand this, the better we can inform interventions and policy initiatives to improve quality of life for these individuals, enhance recruitment and retention in research trials, and ease the translation of AD genetic testing and prevention into clinical practice. The PI of this pilot study is well-positioned to achieve the project's goals: she is leading the development of the process to disclose genetic risk results to participants in the API Generation study.

We need to study why people chose to share or not share knowledge of their genetic risk because we need to understand in what ways, if any, the social aspect of clinical AD generalize to the preclinical state. Clinical AD can lead to serious negative social consequences like punitive stereotypes, alienation, paternalism, and discrimination. As a result, asymptomatic individuals who learn they are at increased genetic risk for this debilitating neurodegenerative disease may conceal this information from family members and others. Alternatively, they may capitalize on benefits of knowing this information, such as the chance to undertake certain health, relationship, financial, and family planning activities. This information may also promote caring and generativity. Alzheimer's disease can, for example, evoke social altruism, which may stimulate emotional and educational support, affection, and positive social interactions. The more we understand this, the better we can translate the progress in research to develop precision medicine for the brain into clinical practice.

The proposed pilot project takes advantage of a unique opportunity to study how learning genetic risk for AD impacts individuals' family and social relationships. Research in this area has focused almost exclusively on how learning AD genetic risk impacts cognitively and affectively on the individual.² This study is highly innovative because no published study has explained how the person with genetic risk for AD is impacted in their relationships. Moreover, it has been designed to gather information on diverse types of relationships, including blood-related family members (who may share the genetic risk) and healthcare providers (who provide routine medical care to the individual). In addition, no published studies have been reported on individuals with different degrees of objective and subjective risk. It builds on research that has shown, for other conditions, both the level of certainty in the test result and uncertainty that remains after learning a result can affect whether individuals share genetic test results.^{2,3,4,5,6,7}

This study will use semi-structured and structured measures to examine decision-making and experiences of sharing of APOE results with key third-party stakeholders (e.g., family, healthcare providers, friends, and employers). Using a mixed methods approach, qualitative data from the proposed study will also be triangulated with quantitative data from the Generation Study.

6. Statistical and experimental fine mapping of Alzheimer's disease loci

PI: Christopher Brown, PhD

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is essentially untreatable. Available drugs for AD are only marginally effective. Currently 5.2 million people in the US have AD. As the population ages, AD cases will increase to 11-16 million in 2050. AD is highly heritable and has a complex genetic architecture. More than two dozen regions of the genome have been shown to affect AD risk. The goal of the proposed research is twofold. First, to develop a novel statistical technique to identify the specific genes at these loci that affect risk. Second, we will experimentally validate these predictions at two selected genes. Achievement of these goals will improve our mechanistic understanding of disease pathology and open avenues for therapeutic development.