Protein variants as blood based biomarkers for diagnosing and staging AD

https://neurodegenerationresearch.eu/survey/protein-variants-as-blood-based-biomarkers-for-diagnosing-and-staging-ad/

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Country

USA

Title of project or programme

Protein variants as blood based biomarkers for diagnosing and staging AD

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NIH (NIA)

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01/09/2016

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1

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 - Extramural... Dementia... Neurodegenerative... Neurosciences... Parkinson's Disease... Prevention

Research Abstract

ABSTRACT There are over 5 million cases of Alzheimer’s Disease (AD) in the US, the number of cases is expected to nearly double over the next 15 years, and the total annual economic costs are over $225 billion. Despite these tremendous costs, there is still no effective treatment for AD. The protein amyloid-beta (Aß) has been linked to AD for many years, but despite thousands of publications on the connection between Aß and AD, there is still much confusion over the role of Aß in AD, and therapeutics targeting Aß have met with very limited success. The protein tau has also been linked to AD. Similar to Aß, tau also exists in a wide variety of different forms in the human brain, so the role of tau in the onset and progression of AD is also not clear. Two other neuronal proteins, alpha-synuclein (a-syn) and Tar-DNA binding protein (TDP-43), have also been implicated in neurodegenerative diseases and play major roles in Parkinson’s disease and Amyotrophic lateral sclerosis (ALS), respectively. All four of these key neuronal proteins, Aß, tau, a-syn and TDP-43, are prone to misfolding and aggregation and small toxic aggregates of each of these proteins are thought to play a role in the onset, progression and spread of a number of different neurodegenerative diseases. Cellular stress caused by toxic aggregates of one protein can induce formation of toxic aggregates of other proteins ultimately resulting in a spectrum of neurodegenerative diseases. Clearly generation and accumulation of toxic protein variants of tau, Aß, TDP-43 and a-syn AD play an important role in the onset and progression of neurodegenerative diseases including AD. Because of the important role of these protein variants in different neurodegenerative disease, we hypothesize that there are distinct toxic protein variant profiles that distinguish AD, and that levels of key protein variants in these profiles will change during progression of AD and also from patient to patient. We hypothesize that by determining each individual’s toxic protein variant fingerprint using biomarkers present in sera or plasma samples, we can facilitate pre-symptomatic diagnosis and staging of AD, identify appropriate therapeutic strategies for each individual patient, and also monitor effectiveness of different therapeutics in real time. The goal of this proposal is to identify blood based biomarker fingerprints that distinguish different stages AD, including presymptomatic AD, and that identify the most appropriate therapeutic strategy for each individual patient. We developed novel technology that enables us to generate antibody fragments (nanobodies) that selectively bind disease related protein variants. We have a panel of 15 nanobodies to different toxic variants of Aß, tau, a-syn and TDP-43 and have shown that we can detect these variants in blood samples of patients suffering from AD, PD and other neurodegenerative diseases, but not in age-matched cognitively normal cases. The aims of this proposal are to utilize our panel of nanobodies that selectively recognize different disease related forms of Aß, tau, a-syn and TDP-43 to characterize a set of longitudinal plasma samples taken from AD and age-matched control patients. These studies will define protein variant fingerprints that not only distinguish AD from cognitively normal controls, but will define different fingerprints for different stages of AD. We will then characterize a larger set of samples from a clinical population to determine protein variant fingerprints that correlate with different clinical symptoms, such as parkinsonism, aphasia and ataxia. Defining the various protein variant fingerprints associated with different stages and clinical manifestations of AD will provide a very powerful tool to facilitate presymptomatic and personalized diagnoses of AD, indicate the most appropriate therapeutic strategy for each individual patient, and provide a means to monitor the effectiveness of the selected therapeutic in real time.

Lay Summary

NARRATIVE Generation of misfolded and aggregated protein variants is a common theme

linking several neurodegenerative diseases including Alzheimer’s (AD) and Parkinson’s diseases, and the presence of specific toxic protein variants has great promise as biomarkers for these diseases. This project will detect the presence of a panel of key toxic protein variants in blood samples from human AD, control and related neurodegenerative disease cases and determine which biomarkers are most effective do diagnosis and stage AD. The project has direct applications to related diseases such as Parkinson’s, Dementia with Lewy Bodies and Amyotrophic Lateral Sclerosis.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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