A Proinflammatory Endophenotype to Predict NSAID Treatment Response Alzheimers Disease Clinical Trials

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A Proinflammatory Endophenotype to Predict NSAID Treatment Response Alzheimers Disease Clinical Trials

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NIH (NIA)

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia...

Neurodegenerative... Neurosciences... Precision Medicine... Prevention

Research Abstract
PROJECT SUMMARY It is our hypothesis that Alzheimer's disease (AD) and mild cognitive impairment (MCI) are heterogeneous conditions and, therefore, a paradigm shift is required to identify specific subpopulations for targeted interventions. This approach has generated significant success in other complex diseases such as cancer and cardiovascular disease. A key opportunity in this context is the identification of those most likely to benefit from non-steroidal anti-inflammatory (NSAID) drugs and other anti-inflammatory compounds. The relation between inflammation and the development of AD, MCI, and cognitive decline has received a great deal of attention with basic science and observational human studies demonstrating a protective effect against cognitive loss. Likewise, in our work, inflammation has been a key mechanism in the biological profile that is indicative of disease presence. Based on a wealth of literature (epidemiological, cross-sectional, pathobiological and animal model), multiple clinical trials have been conducted to determine the utility of NSAID compounds in treating or preventing AD (Alzheimer's Disease Cooperative Study [ADCS] AD and MCI anti-inflammatory trials; Alzheimer's Disease Anti-inflammatory Prevention Trial [ADAPT]); however, each of these studies failed to demonstrate therapeutic benefit, in fact some patients may have exhibited worsening cognitive performance with treatment. Our preliminary data suggests that particular subsets of patients in these trials did benefit from treatment and that our blood-based proinflammatory endophenotype can identify both positive and adverse responders within these trials. Here we propose to leverage three previously conducted clinical trials to test our hypothesis that our blood- based proinflammatory endophenotype can identify the subsets of patients who benefited from these previously conducted clinical trials. By conducting proteomic assays from existing biorepositories from the ADCS and ADAPT, we will address the following Specific Aims: Specific Aim 1. Demonstrate the utility of the proinflammatory endophenotype as a means for patient selection into NSAID therapy for treating and preventing AD; Specific Aim 2. To determine if change in proinflammatory endophenotype scores over time is a biomarker of therapeutic response. By leveraging a highly innovative method and substantial existing resources, the current project addresses a significant need in the search for novel approaches AD therapeutics. The significance of the current project is the identification of a specific subset of patients who will experience clinically significant cognitive benefit from administration of NSAID medication. If successful, the current project will set the stage for a novel clinical trial that enrolls patients specifically based on baseline proinflammatory endophenotype scores for administration of NSAID therapy. In the long-term, this line of research is designed to build a person-centered (i.e. personalized) approach to the treatment of Alzheimer's disease.

Lay Summary
PROJECT NARRATIVE Alzheimer's diseases are a growing public health crisis impacting millions of elders world-wide with a health care cost greater than cancer and equivalent to cardiovascular disease. Current treatments only slow progression of the disease and new strategies are urgently needed. The relevance of the current project is the validation of a person-centered approach to treating Alzheimer's disease by identifying specific subgroups that are most likely to respond to targeted therapies. The outcomes of this project will fundamentally change the approach to the search for novel therapies for AD from the "one-size-fits-all" approach to the search for specific subgroups that can be treated with targeted medications.

Further information available at:

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Investments > €500k

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United States of America

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