Clearance and In Vivo Detection of Tau Pathology

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Country

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Title of project or programme

Clearance and In Vivo Detection of Tau Pathology

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NIH (NIA)

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9

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... Diagnostic Radiology... Immune System... Immunization... Neurodegenerative... Neurosciences... Vaccine Related

Research Abstract

DESCRIPTION (provided by applicant): Amyloid-? (A?) in Alzheimer's disease (AD) is being targeted in several clinical trials, with many being immunotherapies. Findings to date indicate that A? plaque clearance does not slow progression of dementia, emphasizing the need for alternative targets, further supported by the recent failures of Phase III A? antibody trials. Obviously, tau pathology is another important target in AD, and the primary one in other tauopathies. Presence of pathological tau correlates much better with the degree of dementia than A? deposition. Hence, clearing tau may be more effective than removing A? once cognitive impairments are evident, and ideally both these hallmarks of AD should eventually be targeted together prophylactically. On the diagnostic front, single chain variable antibody fragments (scFv's) are attractive as imaging ligands to detect tau lesions in AD or other tauopathies. A? plaque imaging probes derived from ?-sheet binding dyes are already in clinical use, and a few such tau-binding dyes are being evaluated in animals and humans. Antibody-derived probes are likely to provide greater specificity for detecting tau lesions. Furthermore, tract-tracing manganese-enhanced magnetic resonance imaging (tt-MEMRI) is a unique technique to study how tau pathology impairs neuronal transport in live animals, and for monitoring longitudinally the efficacy of related therapies. Specific Aim 1 is to identify the most efficacious active tau immunization approach in transgenic tauopathy mice. We have assessed the efficacy of various phospho-tau immunogens, with the most efficacious one encompassing the P-Ser396, 404 epitope. It is hypothesized that targeting multiple epitopes will enhance efficacy. If not, it woul be clinically safer to immunize with a single epitope as those are less likely to lead to adverse T cell activation. Ideally, this should be clarified prior to clinical trials. Specific Aim 2 is to asess the therapeutic and diagnostic utility of various tau antibody fragments that we have generated using phage display technology. We hypothesize that because of their smaller size, scFv's will be more efficacious than antibodies as therapy or diagnostic PET markers for tau pathology. We have already identified several tau-targeting scFv's that show promise in vitro and in vivo. Specific Aim 3 is to determine if tau immunotherapy can acutely improve neuronal transport in vivo, and/or reverse such impairments. Furthermore, it will be clarified if such improvements correlate with clearance of pathological soluble and/or insoluble tau. We have shown with tt-MEMRI that neuronal transport decreases as tau pathology advances, and that prophylactic active tau immunization improves such transport. We now seek to assess acute and long term benefits of tau antibodies with such imaging. We hypothesize that both approaches (acute, reversal) will improve neuronal transport but only the latter will correlate with clearance of insoluble tau, suggesting that soluble tau is a valid therapeutic target. Overall, these three aims may lead to novel therapies and diagnostic markers for AD and related tauopathies.

Lay Summary

PUBLIC HEALTH RELEVANCE: This proposal seeks to determine: 1) The most efficacious active tau immunization approach for future clinical trials, considering safety issues as well; 2) The therapeutic and diagnostic utility of various tau antibody fragments, and; 3) If tau immunotherapy can acutely improve neuronal transport in vivo, and/or reverse such impairments. Overall, these three aims may lead to novel therapies and diagnostic markers for AD and related tauopathies. Hence, this research is very relevant to public health.

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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