Epitope-Specific Targeting of Tau Aggregates.

https://neurodegenerationresearch.eu/survey/epitope-specific-targeting-of-tau-aggregates/

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Country

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Title of project or programme

Epitope-Specific Targeting of Tau Aggregates.

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NIH (NIA)

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01/09/2011

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

tau aggregation, tau Proteins, Epitopes, Neurofibrillary Tangles, Tauopathies

Research Abstract

DESCRIPTION (provided by applicant): Harnessing the immune system to target pathological tau protein has recently become attractive as a potential therapy for Alzheimer’s disease (AD) and related tauopathies. We previously showed that active immunization targeting a disease-related phospho-tau epitope reduces cerebral tau aggregates in vivo and slows progression of the tangle-related behavioral phenotype. The promise of tau immunotherapy has now been

confirmed by other groups. Recent reports that extracellular tau is important for the anatomical spread of tau pathology strengthen as well the feasibility of clearing pathological tau. While the active approach is in many ways ideal for a chronic disease such as AD, it can inherently lead to autoimmune adverse reactions that may be avoided with passive immunization. It also remains to be thoroughly assessed if a similar therapeutic effect can be obtained with tau monoclonal antibodies (mAbs) alone, as our preliminary findings indicate. These monoclonals should then be humanized for clinical trials. Specific Aim 1 is to determine if the efficacy, safety and mechanism of action of tau mAbs is epitope- dependent. We hypothesize that antibody efficacy in clearing tau aggregates may depend on the epitope being targeted and the stage of tau pathology. The ability of monoclonals against various tau epitopes to prevent or reverse tau aggregation, and associated toxicity and cognitive impairments will be assessed in a novel tangle mouse model that is ideal for this purpose. Concurrently, the mechanism and safety of antibody-mediated clearance of pathological tau will be clarified in live animals and brain slice cultures. Prevention or reversal of tau aggregation and/or downstream pathology may be epitope dependent. Certain tau epitopes are more prominently detected in the early stages of tau aggregation whereas other are generated and/or become accessible for antibody-binding in the later stages of the disease. It is also conceivable that targeting some regions of tau may have toxic effects. These studies are likely to have broad implications. They may clarify sequence of events involved in tau pathology, and identify which regions of the tau protein is best to target for immunotherapy, which may apply to other therapies as well. Furthermore, these experiments should identify a candidate monoclonal for clinical trials. Specific Aim 2 is structural characterization of the lead therapeutic tau mAb for its humanization. This procedure is necessary to reduce the immunogenicity of the antibody, and thereby render it safer for human use. It requires structural characterization of its binding site, and regions not critical for antigen binding can then be replaced with human sequences. The important structural information can also facilitate development of small molecule mimetics for therapeutic or diagnostic use. Together, these aims may lead to a novel therapy for AD and related tauopathies.

Lay Summary
The Aims are to determine if the efficacy, safety and mechanism of action of tau monoclonals is dependent on which region of the tau molecule in tauopathies is being targeted. Subsequently, the structure of the lead antibody will be characterized so that it can in future studies be humanized for clinical trials in individuals with Alzheimer’s disease or other tauopathies. Hence, this research is very relevant to public health.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

Years:
2016

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