Therapeutic Targeting of Abnormal Conformation in Neurodegenerative Disease

https://neurodegenerationresearch.eu/survey/therapeutic-targeting-of-abnormal-conformation-in-neurodegenerative-disease/

Principal Investigators

WISNIEWSKI, THOMAS M

Institution

NEW YORK UNIVERSITY SCHOOL OF MEDICINE

Contact information of lead PI
Country

USA

Title of project or programme

Therapeutic Targeting of Abnormal Conformation in Neurodegenerative Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,700,830.28

Start date of award

01/09/2010

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Amyloid, tau Proteins, Molecular Conformation, Active Immunization, Neurodegenerative Disorders

Research Abstract
? DESCRIPTION (provided by applicant): Alzheimer’s disease [AD] is characterized by Aß

amyloid deposits in the form of extracellular amyloid ß (Aß) plaques and tau protein aggregates in the form of intracellular neurofibrillary tangles (NFT). Soluble oligomeric forms of Aß and tau are the chief mediators of cytotoxicity in AD. Preclinical studies in transgenic mouse models have shown great efficacy of Aß targeting immunotherapy in the prevention of AD but clinical trials have so far failed to show benefits. We plan to test the hypothesis that for therapy to be effective the concurrent targeting of both Aß and tau related pathology is essential. Our novel active immunization approach uses a polymerized peptide derived from the carboxyl terminus of the British amyloidosis (ABri) peptide prepared by the use of glutaraldehyde as a cross linker, that results in a stabilized, predominately ß sheet oligomeric form that does not form fibrils, which we term pBri. We showed that via conformational mimicry, the pBri peptide, in its stabilized oligomeric form, can initiate a conformation selective immune response, which is specific to pathological aggregated/oligomeric conformers of phosphorylated tau and Aß. In the last funding period we have also shown that stimulation of innate immunity via TLR9 can reduce plaques and tau pathology in Tg2576 and 3xTg mice. The specific aims are: 1) Test conformation targeted active immunization with pBri in htau/PS1 Tg and Tg4510 mice with extensive NFT pathology, as well as in a model of Lewy body pathology (tTA/A53Ta-syn) in order to determine if our novel active immunization approach is effective against tau and a-synuclein related pathology. 2) Characterize our panel of monoclonal anti-pathological conformation antibodies using human tissue, Western blots, laser capture microdissection and surface plasmon resonance measurements. The best mAb will be tested in Tg mouse models. 3) We will determine if our method of stimulating innate immunity via TLR9 with CpG is effective at ameliorating vascular amyloid in TgSwDI mice and tau pathology in Tg4510 mice. These planned studies will provide essential data on three therapeutic approaches that concurrently target Aß and tau pathology prior to potential testing in humans.

Lay Summary
PUBLIC HEALTH RELEVANCE: The central hypothesis to be tested in this proposal is that specific immunological targeting of both Aß and tau oligomer related pathology concurrently will result in an effective therapeutic approach for Alzheimer’s disease (AD). We plan to test both active and passive immunization to the shared pathological conformation of tau and Aß oligomers, and we will determine if innate immunity stimulation via Toll-like receptor 9 can reduce both vascular Aß deposits and tau related pathology.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:

N/A