Combining AD Epitope Vaccine with Innate Immunity

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Country

USA

Title of project or programme

Combining AD Epitope Vaccine with Innate Immunity

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,861,321.10

Start date of award

25/09/2004

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

tau Proteins, Natural Immunity, Epitopes, Vaccination, Alzheimer's Disease

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common cause of dementia in the elderly. It is characterized clinically by progressive cognitive decline, eventually resulting in death, usually within 10 years of diagnosis. The neuropathological features of the

disease include depositions of amyloid-? (A?), neurofibrillary tangles (tau), and neuronal loss in affected brain regions. Currently, the predominant theory of the etiology is delineated in the amyloid cascade hypothesis. According to this hypothesis, the accumulations of various forms of soluble and/or insoluble A? have a central role in the onset and progression of AD and lead to the formation of neurofibrillary tau tangles. However, recent clinical studies using biomarkers demonstrated that A? abnormalities precede the tau pathology and cognitive decline by 10 years or more, whereas accumulation of pathological tau correlates with the onset of clinical symptoms. Thus, there is a consensus in the field that A? – based immunotherapeutic(s) can be effective as a prophylactic measure in very early AD (prodromal) and/or in non-symptomatic subjects at risk for AD, while tau-based immunotherapeutic(s) can be used as a therapeutic measure in patients with mild-moderate AD. Accordingly, our team developed three recombinant protein- based epitope vaccines that target pathological A? (AV-1959R), tau (AV-1980R) or A? /tau (AV-1953R) simultaneously and tested the immunogenicity of these vaccines in wild-type mice. Of note, all these vaccines have been constructed on the proprietary universal MultiTEP platform (US patents submitted) that is highly immunogenic in mice, rabbits and monkeys. Based on these published results and preliminary data the goals of this competitive renewal project are to study the efficacy and safety of single and dual vaccines in 3xTg-AD mice that have both A? and tau pathologies. The following 3 aims will be pursued to achieve these goals: In Aim 1 we will test the efficacy of prophylactic vaccination initiated in young 3xTg-AD mice before the onset of AD-like pathology. More specifically, we will study the efficacy of epitope vaccines targeting either A? (AV- 1959R) or tau (AV-1980R) or A? /tau simultaneously (AV-1953R). In addition, we will optimize the vaccination regimen in these experiments. In Aim 2 we are planning to study the efficacy of a therapeutic/prophylactic vaccination regimen in 3xTg-AD mice with established A? -pathology but before the onset of tau pathology. The completion of these studies will allow us to evaluate the therapeutic efficacy of AV-1959R, the prophylactic efficacy of AV-1980R, and therapeutic/prophylactic efficacies of AV-1953R vaccines. Again, in this aim we will optimize the therapeutic/prophylactic vaccination regimen. Finally, in Aim 3 we will study the efficacy of the therapeutic vaccination regimen in 3xTg-AD mice with established AD-like pathology at the start of vaccination. We believe that the completion of all three Aims by our stellar multidisciplinary team including immunologists, vaccine researchers, neuroscientists/cognitive scientists, and molecular biologists can help us to identify the best immunotherapeutic strategy and translate it to the clinic.

Lay Summary

PUBLIC HEALTH RELEVANCE: The neuropathological features of AD include extracellular plaques (composed primarily of A?) and intracellular neurofibrillary tangles (composed primarily of a cytoskeletal protein, tau). Recent clinical studies using biomarkers demonstrated that A? abnormalities precede tau pathology and cognitive decline by 10 years or more, whereas accumulation of pathological tau correlates with the onset of clinical symptoms, so we hypothesize that targeting both biomarkers might be necessary for the prevention/inhibition of disease progression and cognitive decline. Thus, goals of this R01 proposal are (i) to test the efficacy of 3 vaccines (based on the universal and immunogenic MultiTEP platform) targeting pathological A?, tau or A? /tau simultaneously in 3xTg-AD mice possessing both A? and tau pathologies and (ii) to optimize the immunization regimen based on a combination of these prophylactic and therapeutic vaccines.

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