A Mouse Model of Tau Pathology in AD and Other Dementias

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Country

USA

Title of project or programme

A Mouse Model of Tau Pathology in AD and Other Dementias

Source of funding information

NIH (NIA)

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14

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Alzheimer's disease & other dementias

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Research Abstract

DESCRIPTION (provided by applicant): While there have been numerous studies in both mouse

models and in human patients attempting to prevent amyloid formation and deposition, there have been few therapeutic advances in targeting the formation of neurofibrillary tangles or other tau pathologies. Preliminary data from our lab and from a few others have strongly suggested that immunotherapy can be an effective means of prevention of development of tau accumulation in tau transgenic mice. This is a very surprising conclusion, as tau pathology has been seen as an intracellular event, and the likelihood of significant penetration of antibodies into neurons after peripheral administration appeared to be remote. However, at least some monoclonal antibodies to tau appear to be very effective at prevention of development of pathology in at least two different tau transgenic mouse lines. This evidence for efficacy raises many questions that will need to be addressed before this approach can be tested in humans with tauopathies, not the least of which is the nature of the antibody required for efficacy. We propose a classification of monoclonal antibodies to tau that divides available antibodies into four groups based on specificity for pathological tau aggregates, and will test representative members of all four groups. This work will also shed light on the nature of the tau species that is the target of immunotherapy. At this point, it is not even clear if targeting tau is essential for therapeutic success, and systematic studies with non-specific mouse IgG are essential. We have already identified two antibodies (MC1 and PHF1) that have demonstrated efficacy in prevention of development of tau pathology in mice. Extensive studies are already underway to attempt to determine the mechanism of action of these two antibodies. The controversial claim that there is significant penetration of antibodies into CNS neurons in mouse models will be intensively investigated in both mouse models and in cultured neurons from wild type and transgenic mice. New data showing that tau is actively released from cultured neurons and from other cell lines transfected with tau suggests new mechanisms by which antibodies might prove efficacious. We will examine three mechanisms which have been proposed to explain the efficacy of tau immunotherapy.

Lay Summary
PUBLIC HEALTH RELEVANCE: Neurofibrillary tangles are a major feature of Alzheimer’s disease and several related disorders. There is preliminary evidence that monoclonal antibodies to tau can reduce the rate of development of tangles in some transgenic mouse models, but there is an urgent need to identify the most appropriate antibodies for treatment of human disease. This project proposes systematic testing of different classes of monoclonal antibodies to tau, and to attempt to understand how and why such therapy may be effective.

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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