Multiple Approaches to Abeta Vaccination in Animal Models

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Multiple Approaches to Abeta Vaccination in Animal Models

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1

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Parkinson's disease & PD-related disorders|Alzheimer's disease & other dementias

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Research Abstract

DESCRIPTION (provided by applicant): Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Careful neuropathological studies have shown that aggregations of ?-syn, Aß and tau appear in the same neuronal structures, providing a

pathological basis for the clinical observations of the overlap between PD/DLB and AD. Studies with transgenic (Tg) mice with neuronal expression of human Aß and ?-syn the doubly Tg mice resembled the Lewy-body variant of Alzheimer's disease (39). These mice had severe deficits in learning and memory, developed motor deficits before ?-syn Tg mice, and showed prominent age-dependent neurodegeneration. More recently, mutant (A53T) ?-syn Tg mice were crossed onto 3xTg-AD Tg mice (DLB-AD mice). The DLB-AD mice exhibit accelerated cognitive decline associated with a dramatic enhancement of Aß, tau, and ?-syn pathologies (40). Thus approaches that promote the clearance of ?-syn may provide therapeutic benefit for PD and DLB, as well as AD. Two studies have now shown that active and passive anti-?-syn immunotherapy can decreased aggregated ?-syn in neuronal cell bodies and synapses and improve behavior (1, 2). In this competitive renewal the goals are to design multi-epitope anti-?-syn DNA vaccines and test their therapeutic potential in Tg models that develop human-like neuronal ?-syn pathology and mixed pathology. To fully achieve these goals we propose the following 4 Aims: Aim 1: Fine mapping of the B-cell and T-cell epitope(s) of ?-syn in response to DNA Immunization. We will analyze the B- and T- cell immune responses to anti-?-syn DNA Immunization in wild-type mice. Mice will be vaccinated with DNA encoding full-length human ?-syn protein. Anti-?-syn titers and the B-cell and T-cell epitopes will be identified. Aim 2: Testig of candidate multiple-epitope DNA vaccines in wild-type mice. A multi-epitope design where ?-syn B-cell epitopes (12, 15, 52, 54) will be fused with PADRE and as the foreign T helper cell epitopes. Both antibody titers and affinity will be measured. Aim 3. Testing prophylactic and therapeutic efficacy of ?-syn DNA epitope vaccines Tg mice. Human wild-type ?-syn (hSYN line D) mice (3) will be used. We will assess the ability of the best multi-epitope vaccines to induce ""protective"" immune response in pre-pathology 2 months old hSYN Tg mice, and ""therapeutic"" response to pre-existing ?-syn pathology in 6 months old hSYN Tg mice. Aim 4. Testing the efficacy of ?-syn DNA epitope vaccine(s) in mixed pathology Tg mice. We will test the ability of the best multi-epitope ?-syn DNA vaccine to induce ""protective"" immune response in pre-pathology 2 months old mixed pathology DLB-AD Tg mice. The DLB-AD mice exhibit accelerated cognitive decline associated with a dramatic enhancement of Aß, tau, and ?-syn pathologies. Immunized DLB-AD Tg mice will be compared against non-immunized mice for cognitive decline and Aß, tau, and ?-syn pathologies. Finally, we will compare the best multi-epitope ?-syn DNA vaccine against our best multi-epitope Aß DNA vaccine in the mixed pathology DLB-AD Tg mice (40).

Lay Summary

Mixed brain pathologies account for most dementia cases in community-dwelling older persons, and careful neuropathological studies have shown that aggregations of alpha-synuclein, amyloid-beta and tau proteins appear in the same neuronal structures, providing a pathological basis for the clinical observations of the overlap between dementia with Lewy bodies disease (DLB) and Parkinson's disease (PD) and Alzheimer's disease (AD). Taken together, these studies indicate that the pathological process of PD and DLB may accelerate that of AD, while that of AD may also drive PD and DLB. In this competitive renewal we propose to utilize advanced immunotherapeutic strategies to target alpha-synuclein neuropathology. Thus the goal is to design multi-epitope anti-alpha-synuclein DNA vaccines, and test their effectiveness in transgenic mouse models that develop human-like neuronal alpha-synuclein pathology, as well as in mixed pathology transgenic mice with alpha-synuclein pathology and amyloid-beta and tau pathology. In summary, our advanced multiple component DNA vaccine designs are engineered to promote a strong anti-alpha-synuclein antibody response without the risk of producing an

adverse autoimmune response.

Further information available at:

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Investments > €500k

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United States of America

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