Immune-Mediated Mechanisms underlying CNS Abeta Clearance

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Country

USA

Title of project or programme

Immune-Mediated Mechanisms underlying CNS Abeta Clearance

Source of funding information

NIH (NIA)

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14

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders... Dementia... Immune System... Immunization... Neurodegenerative... Neurosciences... Prevention... Translational Research... Vaccine Related

Research Abstract

DESCRIPTION (provided by applicant): There is compelling evidence that accumulation of A¿ aggregates plays a pivotal role in Alzheimer’s disease (AD); thus, multiple strategies targeting A¿ are being developed as therapeutics. Numerous preclinical studies demonstrate the therapeutic potential of targeting A¿ by active or passive immunization paradigms. Although anti-A¿ immunotherapies remain mainstays of disease modifying therapies being tested in humans, it is our general premise that current agents represent first generation therapeutics with suboptimal properties and that the therapeutic potential of immunotherapy can be dramatically improved by both enhancing the understanding of how immunotherapies work and by developing alternative biological immunotherapies. Indeed, there remain a number of unanswered questions regarding both mechanism of action and pharmacokinetics of A¿ immunotherapies that are critical to address in order to optimize the approach. Herein, we propose three distinct, but interrelated, aims that will further explore aspects of A¿ immunotherapy. The experiments in Aim 1 represent a shift from previous studies in the area of AD immunotherapy. As opposed to using antigen specific antibodies targeting A¿ we will harness soluble Toll Like Receptors (sTLRs) as decoy innate immune pattern recognition receptors to therapeutically target amyloid and amyloid-like aggregates. The studies in Aim 2 stem from data showing that pro-inflammatory stimuli attenuate and anti-inflammatory stimuli promote A¿ deposition. We, therefore, propose that preexisting alterations in the innate immune activation state that are present in the aged human brain, but not as much in APP mice, might dramatically alter the efficacy of anti- A¿ immunotherapy. We will evaluate this hypothesis by exploring how pro- or anti-inflammatory “”preconditioning”” of the brain alters efficacy of anti- A¿ immunotherapy. In Aim 3 we will determine the cycling time of anti- A¿ antibodies between the brain and periphery and identify parameters that regulate this process. Establishing the cycling time is critical to understand the pharmacokinetics that regulate antibody exposure in the brain and has major conceptual ramifications regarding development of immunotherapies for A¿ and other CNS targets.

Lay Summary

PUBLIC HEALTH RELEVANCE: Finding effective therapy for Alzheimer’s disease is a huge unmet medical need. The proposed studies will provide key information that will help guide development and optimization of current immunotherapies and provide the rationale for further development of novel therapies harnessing innate immune receptors that could target multiple pathologies relevant to Alzheimer’s disease.

Further information available at:

Types:
Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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