# Drug Discovery against the Early, Secreted and Toxic Tau in Alzheimers Disease

https://www.neurodegenerationresearch.eu/survey/drug-discovery-against-the-early-secreted-and-toxic-tau-in-alzheimers-disease/

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**Country**

USA

**Title of project or programme**

Drug Discovery against the Early, Secreted and Toxic Tau in Alzheimers Disease

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NIH (NIA)

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3

**The project/programme is most relevant to:**

Alzheimer's disease & other dementias

**Keywords**

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

**Research Abstract**

DESCRIPTION (provided by applicant): Prevalence of Alzheimer's disease (AD) may quadruple worldwide by 2050, but there is no effective treatment available. The AD hallmark lesions are plaques made of A? peptides and tangles of phosphorylated tau (p-tau). [A? immunization has effectively eliminated its target in brains even in AD patients, albeit questions remain about its efficacy and trial design. Tauopathy correlates well with memory decline in AD and also is a defining feature of other tauopathies. Moreover, active or passive immunization against p-tau tangle epitopes or tau seeding shows promising efficacy in mouse models. However, since neuronal dysfunction long precedes tangle formation, immunotherapies specifically against the early pathogenic pretangle events that lead to memory loss in AD are being actively pursued.] Notably, an early event in AD tauopathy is tau hyperphosphorylation especially on Ser/Thr-Pro motifs. We have previously found that the phosphorylated Thr231-Pro motif in tau (pT231-tau) exists in the cis and trans conformations, and also identified the unique prolyl isomerase Pin1 to accelerate their conversion to prevent p-tau misfolded and inhibit tauopathy. Furthermore, Pin1 is inhibited by multiple mechanisms in human MCI and AD neurons, whereas the Pin1 SNP that prevents its down-regulation is associated with delayed AD onset. In addition, human Pin1 is located at 19p13.2 associated with late-onset AD pT231-tau is at the beginning of sequential p-tau epitopes in AD pretangle neurons and pT231-tau in CSF correlates with memory loss and tracks MCI conversion to AD. These results suggest that pT231-tau is a very early disease-initiating event in AD. [We have recently developed a novel technology to generate the first cis and trans pT231-tau polyclonal antibodies, and identified the previously unrecognized early pathogenic cis tau that leads to tauopathy in MCI and AD. We now created neutralizing mAb that effectively removed this early, secreted and toxic cis tau in vitro, ex vivo and in mice. Thus, this proposal is designed to test our novel hypothesis that neutralizing conformation-specific mAbs and vaccines against only the early, secreted and toxic cis p-tau while leaving the healthy trans untouched may be highly efficacious and specific in halting or even preventing tauopathy in AD. Aim 1 will further identify the best cis and trans mAbs and evaluate their efficacy and mechanisms in neutralizing the ability of p-tau to induce and spread neurotoxicity in vitro and ex vivo. Aim 2 will evaluate the effects of cis and trans pT231-tau mAbs on tauopathy in two different but complementary mouse models of tauopathy. Aim 3 will develop and evaluate the effects of cis and trans pT231-tau vaccines on tauopathy in two mouse models of tauopathy. The expected outcomes would constitute innovative conformation-specific immunotherapies against the very early, secreted and toxic cis pT231-tau in tauopathy, raising the unique opportunity of halting or preventing tauopathy and memory loss in AD patients at early stages. This research can offer a unique approach for therapeutics directed specifically against the early pathogenic misfolded proteins in AD.]

**Lay Summary**

PUBLIC HEALTH RELEVANCE: The prevalence of Alzheimer's disease increases rapidly as people live longer, but currently there is no effective treatment. Since Alzheimer's disease may take more than a decade to develop, therapies that specifically target early pathogenic events are sorely needed for this devastating disease. As a proof of concept, we have discovered [the early, secreted and toxic tau that leads to tau pathology and memory loss in Alzheimer's disease, and here describe the development of innovative neutralizing antibodies and vaccines specifically against only this early, secreted and toxic tau] while leaving healthy tau untouched to inhibit tau pathology and halt memory loss at an early step for treating Alzheimer's disease. We believe that these studies might lead to a novel class of immunotherapy for Alzheimer's

disease.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Alzheimer's disease & other dementias

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