# Linking Tau Structure to Its Functions and Mechanisms in Alzheimer’s Disease

https://neurodegenerationresearch.eu/survey/linking-tau-structure-to-its-functions-and-mechanisms-in-alzheimer%c2%92s-disease/

**Principal Investigators**

BLOOM, GEORGE S

**Institution**

UNIVERSITY OF VIRGINIA

**Contact information of lead PI**
**Country**

USA

**Title of project or programme**

Linking Tau Structure to Its Functions and Mechanisms in Alzheimer’s Disease

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

€ 1,696,620.18

**Start date of award**

01/08/2016

**Total duration of award in years**

1

**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... Clinical Research... Clinical Research - Extramural... Dementia... Neurodegenerative... Neurosciences

**Research Abstract**

? DESCRIPTION (provided by applicant): The most conspicuous molecular and histological landmarks of Alzheimer’s disease (AD), excess brain levels of amyloid-? (A?) peptides and abnormally phosphorylated tau, and their respective accumulation into plaques and tangles, have been known for many years. Because mutations that increase total A? or specific, excessively toxic A? variants can cause AD, nearly all efforts to develop effective, disease modifying drugs for AD have been directed at reducing the A? burden in brain. Unfortunately, no such efforts have yet yielded compounds that are sufficiently safe and efficacious to gain FDA approval. To get past this seemingly unscalable wall that has thwarted all efforts to conquer AD so far, new approaches are needed. One such approach is to unravel the seminal signaling pathways that convert normal healthy neurons into neurons that will die before the AD patients themselves. To that end, we recently made major strides towards understanding what may be the most common pathway for neuron death in AD: ectopic cell cycle re-entry (CCR). Whereas fully differentiated normal neurons have permanently exited the cell cycle, up to 5-10% of the neurons in brain regions affected by AD show signs of CCR. These neurons never divide, but instead eventually die and may account for up to 90% of the neuron loss in AD. Building on a prior report that A? oligomers (A?Os) can induce this ectopic CCR, we found that the mechanism is tau-dependent, and entails activation of 4 protein kinases, fyn, mTOR, PKA and CaMKII, which must respectively lead to tau phosphorylation at Y18, S262, S409 and S416. All of this occurs less than a day after exposure of neurons to A?Os. These activated kinases and phospho-tau epitopes represent potential very early biomarkers for AD, and the kinases also represent potential new therapeutic targets. Although we have now defined many steps of the CCR signaling network, a key issue that remains unresolved is why tau phosphorylation at multiple specific sites is necessary to drive post-mitotic neurons back into the cell cycle. Based on this background we propose to use primary mouse neurons, and brain tissue derived from transgenic mice and humans to address 2 interrelated questions. 1) How does tau phosphorylation alter tau structure in a way that enables CCR? 2) By what mechanism does appropriately phosphorylated tau cause CCR? Although the experiments proposed here have been designed in the context of A?O- induced CCR, which is probably unique to AD, tau pathology and neuronal CCR are commonly observed in many other prominent neurodegenerative disorders, such as Parkinson’s disease, Huntington’s disease and frontotemporal dementias. The successful completion of the project proposed here may therefore be relevant at the basic science level and clinically not only to AD, but to several non-Alzheimer’s tauopathies as well.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: In 2014, more than more than 5 million Americans were estimated to have Alzheimer’s disease (AD), which recently surpassed cancer and heart disease as the most costly disease in the US. Disease modifying drugs for AD are now lacking, as are methods to detect the disease accurately in its early stages. Unless both of these limitations can be overcome soon, the number of AD cases in the US is likely to rise 2-3-fold by the middle of the 21st century, and AD will potentially bankrupt the US national health care system.

**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