

# The hsp90 Cochaperone FKBP51 Regulates tau Structure and Function

<https://www.neurodegenerationresearch.eu/survey/the-hsp90-cochaperone-fkbp51-regulates-tau-structure-and-function/>

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### Country

USA

## Title of project or programme

The hsp90 Cochaperone FKBP51 Regulates tau Structure and Function

## Source of funding information

NIH (NIA)

## Total sum awarded (Euro)

€ 2,190,243.12

## Start date of award

01/04/2011

## Total duration of award in years

1

## The project/programme is most relevant to:

Alzheimer's disease & other dementias

## Keywords

Tacrolimus Binding Proteins, tau Proteins, Molecular Chaperones, tau aggregation, tacrolimus binding protein 4

## Research Abstract

? DESCRIPTION (provided by applicant): Recent evidence suggests that intermediate

oligomers of the microtubule-associated protein tau are more neurotoxic in tauopathies than densely packed  $\beta$ -sheet fibrils. However, this remains unproven because relevant mechanisms to trap distinct assemblies of tau aggregates have been lacking. Here we will fill these gaps in our knowledge by using the Hsp90/co-chaperone machinery to control tau structure and assembly to prove how tau aggregate structure relates to its toxicity. Our team showed that tau physically interacts with the chaperone Hsp90, providing the first 3-dimensional structure of a client complexed with Hsp90. While Hsp90 levels are largely static in the aging brain, a group of co-chaperones that can interface with tau through Hsp90 are much more dynamic; some rise and others fall during a lifetime. We have found that Hsp90 and one of the rising co-chaperones, the cis/trans peptidyl-prolyl isomerase (PPIase) FK506 binding protein 51 (FKBP51), coordinate to provoke tau pathogenesis by reducing tau  $\beta$ -sheet amyloidosis. This corresponded with increased oligomerization and neurotoxicity in tau transgenic mice. Thus, we speculate that the Hsp90 complex controls whether tau aggregates into toxic or benign species depending on the associated co-chaperones. In fact, we now have evidence that just as FKBP51 levels increase in the aging brain, so do the levels of a second Hsp90-associated PPIase, cyclophilin 40 (Cyp40/PPID), to an even greater extent than FKBP51. And just like FKBP51, Cyp40 reduces tau aggregation and produces amorphous intermediates. Now, we have also discovered that two other co-chaperones, Aha1 and FKBP52, which decrease in the aging brain, actually enhance the  $\beta$ -sheet propensity of tau. With these tools, we can now test the hypothesis that tau toxicity arises due to structural changes in tau assemblies brought on by the Hsp90/co-chaperone system. To test this, we will determine if Hsp90/co-chaperone complexes that promote tau oligomer formation inevitably lead to toxicity. We will then determine if Hsp90/co-chaperone complexes that stimulate tau amyloidosis prevent its toxicity. Lastly we will determine the impact of Hsp90/co-chaperone complexes that favor tau amyloid or oligomer production on functional deficits in a mouse model of tauopathy. We anticipate that we will identify ways to regulate tau aggregation using the dynamic Hsp90 complex, which will allow us to home in on structures of toxic tau intermediates. We also will determine whether distinct Hsp90/co-chaperone complexes can differentially triage aberrant tau in the brain, possibly allowing us to improve the specificity of therapeutics targeting this mechanism.

### **Lay Summary**

**PUBLIC HEALTH RELEVANCE:** Abnormal accumulation of the microtubule associated protein tau in the brain is thought to be a major cause of the symptoms and neuronal loss observed in neurological disorders called tauopathies. This proposal aims to evaluate the ability of the molecular chaperone machinery to control tau accumulation in the brain.

### **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