

# Klotho and Neurodegenerative Disease

<https://www.neurodegenerationresearch.eu/survey/klotho-and-neurodegenerative-disease-2/>

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### Country

USA

## Title of project or programme

Klotho and Neurodegenerative Disease

## Source of funding information

NIH (NINDS)

## Total sum awarded (Euro)

€ 1,568,997.25

## Start date of award

01/04/2016

## Total duration of award in years

5

## The project/programme is most relevant to:

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

## Keywords

alpha synuclein, resilience, Amyloid beta-Protein, Parkinson Disease, Neurodegenerative Disorders

## Research Abstract

? DESCRIPTION (provided by applicant): Cognitive decline due to neurodegenerative disease is emerging as one of our greatest biomedical challenges – a problem for which we have no effective medical therapies. Klotho is a longevity-promoting hormone that circulates throughout the body and brain following cleavage from its membrane form. We recently found that

widespread, genetically-driven increases in klotho over the lifespan enhanced cognition in normal mice, in part through synaptic enrichment of key learning and memory molecules. In parallel with mice, we found that individuals with higher levels of systemic klotho, due to a genetic variant, showed better than average cognitive functions. We then tested whether the beneficial effect of klotho extends to neurodegenerative disease-related deficits and pathologies in mouse models. Indeed, transgenic klotho elevation enhanced cognition in mice that model aspects of both Alzheimer's (AD) and Parkinson's disease (PD). These findings are important since cognitive deficits are a key manifestation of both diseases, and even contribute to motor dysfunctions in PD. Our new data suggest that klotho confers cognitive resilience in a diseased brain, possibly through mechanisms that converge upon targets of A $\beta$  and  $\alpha$ -synuclein toxicity – such as at the synapse. Synapses are targeted by the pathophysiology of AD and PD, enriched by klotho, and central to neural communication and function. Thus, understanding klotho-induced structural and molecular changes to the synapse will be a convergent point in dissecting its mechanisms of resilience. We hypothesize that klotho confers cognitive resilience against deficits related to neurodegenerative disease through mechanisms of synaptic enrichment. We will pursue three aims. 1) In Aim 1, we will characterize effects of klotho on resilience to A $\beta$  and  $\alpha$ -synuclein 2) In Aim 2 we will explore molecular targets at the synapse that orchestrate resilience 3) In Aim 3, we will profile key associations in human disease. These studies could fundamentally advance our understanding of cognitive resilience and how klotho confers this effect against converging targets of A $\beta$  and  $\alpha$ -synuclein at the synapse. They could also, directly, lead to the development of urgently needed treatments for cognitive dysfunction that “boost resilience” in neurodegenerative conditions like AD and PD.

### **Lay Summary**

**PUBLIC HEALTH RELEVANCE:** Klotho is a pleiotropic protein that enhances baseline cognitive functions. This proposal investigates klotho and its potential to confer resilience against deficits related to neurodegenerative diseases including Alzheimer's and Parkinson's disease. Since we have no effective medical therapies for cognitive decline due to these diseases, this line of investigation may lead to new ways of boosting an ailing brain.

### **Further information available at:**

#### **Types:**

Investments > €500k

#### **Member States:**

United States of America

#### **Diseases:**

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

#### **Years:**

2016

#### **Database Categories:**

N/A

#### **Database Tags:**

N/A