

# A system approach to targeting innate immunity in AD

<https://www.neurodegenerationresearch.eu/survey/a-system-approach-to-targeting-innate-immunity-in-ad/>

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### Country

USA

## Title of project or programme

A system approach to targeting innate immunity in AD

## Source of funding information

NIH (NIA)

## Total sum awarded (Euro)

€ 7,786,533.03

## Start date of award

20/09/2013

## Total duration of award in years

4

## 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)... Biotechnology... Brain Disorders... Dementia... Genetics... Immune System... Neurodegenerative... Neurosciences... Translational Research

## Research Abstract

DESCRIPTION (provided by applicant): An invariant feature of the pathological cascade in Alzheimer's diseases (AD) is a reactive gliosis, reflecting an underlying alteration in the innate immune activation state within the brain. Innate immune signaling is altered early in AD, but is also skewed towards an activated state as a consequence of brain aging. There is strong genetic evidence that innate immunity has a significant role in AD. Variants in two genetic loci that play roles in the complement cascade, CR1 and CLU, show significant genetic associations with AD, and rare coding variants in TREM2 also confer substantial risk for AD. Numerous experimental studies in AD mouse models show that manipulating innate immune pathways can have positive or negative effects on proteostasis, cognition and neurodegeneration. At least when assessing A $\beta$  pathology as an endpoint, the beneficial effects of some innate immune system manipulations are robust. We propose to identify therapeutic targets within the innate immune signaling cascade in AD that could be safely manipulated to provide disease modification in AD. However, because of the complexity of, and the gaps in our knowledge regarding, innate immune signaling within the CNS, a systems level approach that integrates multiple types of data will be required to achieve this goal. Indeed, development of any innate immune therapy will need to be finely tuned and extensively validated in order to be further developed as a potential AD therapy. We will use a multifaceted systems level approach to identify targets within innate immune signaling pathways that can safely provide disease modifying effects in AD. Comprehensive, transcriptomic, genetic and pathological data from both humans and mouse models will be generated, integrated and analyzed in novel ways. This integrated data will then be used to guide multiple preclinical target validation studies of key innate immune targets in both APP and tau mouse models as well as non-transgenic mice. These studies will dramatically accelerate the identification and validation of disease modifying innate immune modulatory strategies in AD and will provide important insights into how these various manipulations of innate immune activation states alter normal behaviors with an emphasis on cognition.

### **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 guide development of innate immune therapies. They will provide the rationale and preclinical validation for further development of novel therapies harnessing innate immunity that could target multiple pathologies relevant to Alzheimer's disease.

### **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