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NEW FUNDED PROJECT

New study is funded by the Alzheimer's Association (Chicago, IL, USA) under the grant agreement AARG-21-847642

Title of the study: **"Targeting KLK6 for the treatment of Alzheimer's disease"**

Acronym: K6AD

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Collaborators:

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The study aims to provide preclinical proof-of-concept for targeting the KLK6 protease for treatment of Alzheimer's disease (AD), a devastating neurodegenerative disorder that severely compromises the health and quality of life of affected patients and largely impacts on their families. Current approaches, such as acetylcholinesterase inhibition, *etc*, are applied to treat AD symptoms but do not represent effective causative therapies. The recent targeting of Aβ and tau yielded conflicting results in clinical trials, for example, the anti-Aβ humanized monoclonal antibody solanezumab failed to show promise. Thus, therapeutic strategies that target the underlying disease mechanisms are urgently needed. On the other hand, KLK6 is a neuronal serine protease that recognizes a quite limited number of specific protein substrates among which, notably, the α-synuclein and the APP. KLK6 it thought to have amyloidogenic potential by promoting the *N*-terminal truncation of Aβ, thereby, promoting the accumulation of amyloid deposits. Of note, the concentration of KLK6 is increased in CSF of AD patients relative to healthy controls. To assess the functional implication of KLK6 in AD and validate it as a drug target, we will cross 5XFAD mice (a well-recognized model for AD) with *Klk6*$^{-/-}$ mice that we have generated and characterized, in order to generate 5XFAD*Klk6*$^{-/-}$ mice, with the aim to test whether complete elimination of Klk6 in the AD background will rescue (or partially improve) AD pathology. If, indeed, KLK6 has amyloidogenic potential *in vivo*, we anticipate significant improvement of the AD phenotype of 5XFAD mice at the behavioral, histological, and molecular levels. The expected results could further be exploited for treatment of other dementias given that KLK6 is increased in vascular dementia, and various findings suggest its functional implication in the disease.

https://www.alz.org/research/for_researchers/grants/funded-studies-details?FundedStudyID=2532