Characterizing and Targeting Pyk2 Kinase in Alzheimer’s Disease

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Principal Investigators

STRITTMATTER, STEPHEN M

Institution

YALE UNIVERSITY

Contact information of lead PI
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USA

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Characterizing and Targeting Pyk2 Kinase in Alzheimer’s Disease

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1

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Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

SUMMARY Central to the pathophysiology of cognitive dysfunction in Alzheimer’s disease (AD) is loss of synapses with an impairment of plasticity at surviving synapses. Therapeutic efforts to intervene in AD have focused on the Aß peptide as an upstream trigger for synaptic disease, but clinical trials have been disappointing so far. Additional validated targets for AD therapy are needed, in particular those focused more directly on synaptic deficits. By their very nature, genetic studies of Late Onset AD (LOAD) risk are of direct clinical relevance. The largest GWAS analysis of LOAD identified a short list of genes whose common variants alter risk, providing potential new targets for AD therapy. We considered whether any of these might be directly linked to synaptic dysfunction in AD. Nearly all of the LOAD risk genes are hypothesized to bind Aß, to alter Aß metabolism, to regulate cellular endocytosis, or to modulate immune function. Therefore, their action on synaptic dysfunction must be considered indirect, via Aß levels or via the immune reaction to pathology. From the list of AD genetic risk factors, Pyk2 (also PTK2B or FAK2) is the only gene recognized to encode a protein concentrated at post- synaptic densities with direct effects on synaptic plasticity. Here, we seek to assess the role of Pyk2 in AD genetically and mechanistically, and to evaluate the protein as a therapeutic target focused on synaptic dysfunction. Previously, we have studied the biochemical basis for Aß oligomer (Aßo) toxicity in neurons and these studies have also implicated Pyk2. Using an unbiased genome-wide screening method we searched for Aß oligomer- specific binding sites expressed in brain, and identified PrPC. We defined an Aßo–PrPC–mGluR5–Fyn cascade that damages synapses in AD models. Importantly, the Pyk2 protein physically associates with mGluR5 and Fyn, as well as being implicated in synaptic plasticity. We will evaluate the hypothesis that Pyk2 is essential for manifestations of human familial AD transgene phenotypes in mice, and we will assess Pyk2 dysregulation in human AD samples. We will also target the enzyme pharmacologically. These studies have the potential to couple a validated LOAD genetic risk to synaptic dysfunction in AD, and may establish a connection with the Aßo–PrPC–mGluR5–Fyn cascade. Critically, these data may guide attempts to develop pharmacological tools to target the synaptic Pyk2 pathway for therapeutic intervention in AD.

Lay Summary

PROJECT NARRATIVE Disease-modifying therapy for Alzheimer’s disease (AD) remains a massive unmet medical need. Therapies that preserve synaptic function in AD are crucial. Genetic risk studies of AD have identified one protein that may be directly linked to synapse loss in AD, namely Pyk2. Here, we will evaluate the genetic and mechanistic role of Pyk2 in synapse stability and plasticity, and its role in AD models. We will target the enzyme therapeutically in preclinical studies to evaluate its potential for AD modification.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

Years:
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