Pathway discovery, validation and compound identification for Alzheimers disease

https://neurodegenerationresearch.eu/survey/pathway-discovery-validation-and-compound-identification-for-alzheimers-disease/

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Country

USA

Title of project or programme

Pathway discovery, validation and compound identification for Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 12,393,509.17

Start date of award

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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... Clinical Research... Clinical Research - Extramural... Dementia... Genetics... Human Genome... Neurodegenerative... Neurosciences... Prevention... Stem Cell Research... Stem Cell Research - Induced Pluripotent Stem Cell... Stem Cell Research - Induced Pluripotent Stem

Cell - Human... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): The overall goal of the proposed study is the discovery and preclinical validation of novel targets associated with molecular processes that lead to cognitive decline, the primary outcome of most AD trials. The recent NIA Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention that led to the RFA to which we are responding, made a number of recommendations which motivated the strategy adopted in the proposed study. Our proposal brings together an exceptionally strong and unique multi-disciplinary team with the relevant skills needed to achieve our overall goal. In Aim 1, we take a systems biology approach to mine a truly unique set of deep clinical, paraclinical, pathologic, genomic, epigenomic, and transcriptomic data assembled from frozen dorsolateral prefrontal cortex brain tissue of 1000 subjects from two cohort studies of aging and dementia, the Religious Order Study and the Memory and Aging Project, in conjunction with other publicly available functional datasets. These unique data provide an excellent substrate for the identification and nomination of molecular targets for drug discovery. Target discovery is coupled with a flexible translational strategy that first validates targets by a targeted proteomic study of brain tissue from the same region and subjects in Aim 2. In Aim 3, an RNA interference (RNAi) and overexpression functional validation study in cultured human neurons and astrocytes is executed in parallel in Aim 3. Finally, these data come together in Aim 4 which performs high throughput small molecule screens on neurons and astrocytes derived from induced pluripotent stem cells (iPSC) on the most promising targets. Our proposal is ambitious but realistic: it reflects the deployment of cutting-edge approaches with a practical mindset in which redundancies have been carefully considered to mitigate risk and ensure the delivery of data, network models and lead compounds. The proposed study will discover and validate novel targets associated with molecular processes that lead to cognitive decline, and it will demonstrate the druggability of one or more targets, setting the stage for clinical trials with new and novel approaches to the prevention and treatment of AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: The prevention and treatment of AD is a major public health priority. However, novel therapeutic targets are urgently needed. The proposed study will leverage deep phenotypic and multi-level “”-omics”” data to identify novel therapeutic targets, functionally validate and subsequently demonstrate the druggability of a number of selected targets, thereby filling an important gap between the new generation of “”-omics”” technology and the identification of novel and druggable targets to move to preclinical or clinical trials.

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