Identification of Old-Age-Associated Alzheimers Disease Drug Targets

https://neurodegenerationresearch.eu/survey/identification-of-old-age-associated-alzheimers-disease-drug-targets/

Principal Investigators

SCHUBERT, DAVID R

Institution

SALK INSTITUTE FOR BIOLOGICAL STUDIES

Contact information of lead PI
Country

USA

Title of project or programme

Identification of Old-Age-Associated Alzheimers Disease Drug Targets

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,211,422.02

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01/05/2014

Total duration of award in years

3

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... Neurodegenerative... Neurosciences... Prevention... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): Old age is by far the greatest risk factor for the majority of neurodegenerative diseases, yet few attempts have been made to identify aging-associated therapeutic targets for any of these diseases, including Alzheimer's dementia (AD). During the last ten years the Salk laboratories have developed nerve cell culture drug screening assays that are based upon old-age-associated CNS pathologies, including the loss of trophic support, reduced energy metabolism, oxidative damage, and the accumulation of intracellular aggregated proteins. Using these assays in conjunction with iterative medicinal chemistry, an exceptionally potent compound, called J147, was made that is neuroprotective in all of the above assays with EC50s in the low nanomolar range. This compound also enhances memory in young and very old (30 mo) mice, improves cognitive function and synaptic structure in old (23 mo) AD transgenic mice, and extends the life span of flies. SinceJ147 prevents cell death in multiple cell culture models that lack any of the recognized AD drug targets of the amyloid pathway, it must be acting on highly relevant molecular target(s) and target pathways that are unrelated to the amyloid pathway and that contribute to its therapeutic efficacy. Given that J147 is neuroprotective in multiple, functionally distinct, age-associated toxicity assays, it should be possible to define common, shared neuroprotective pathway(s) which will then be used as the basis for identifying new therapeutic targets for the treatment of AD. This proposed chemical biology approach to identify drug targets originated in 1785 with the isolation of digoxin from foxglove, followed by morphine from poppies in 1806, and aspirin from salicylic acid in 1897. Not only did these molecules make tremendous contributions to medicine, they also were the key factors in the ++ identification of the molecular pathways and drug targets involving the Na - K -ATP pump, opiate receptors, and the cyclooxygenase enzymes, respectively, leading to a succession of derivative drugs that are in the clinic today. The overall goal of this application i to use a chemical biology approach based upon the J147 compound to identify and validate novel, old-age-associated targets for AD treatment and prevention. This will be done by using molecular biology and proteomics to define the shared molecular signaling pathways that lead to neuroprotection in multiple toxicity assays, and chemistry and proteomics to isolate the molecular target(s) of J147. In vivo target validation will be done in part in an animal model that is not biased toward the familial AD/amyloid pathway, but rather reflects most aspects of human aging and AD, the senescence-accelerated SAMP8 mice.

Lay Summary

PUBLIC HEALTH RELEVANCE: Currently there are no effective drugs that prevent the death of nerve cells associated with age- dependent neurodegenerative diseases such as Alzheimer's. These diseases are very complex and there are many factors that contribute to the patient's demise, yet most drug discovery projects are using an approach that only addresses one of the many aspects of the disease pathology. In this proposal, we are using a highly potent drug that inhibits multiple old age-associated toxicities that have not been explored by the pharmaceutical industry, each one of which may contribute to the disease, to identify unique targets for AD therapeutics, which is the goal of this RFA.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:

Alzheimer's disease & other dementias

Years:
2016

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N/A

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