Allopregnanolone a Regenerative Therapy for Alzheimers: FDA-Required Toxicolog

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Country

USA

Title of project or programme

Allopregnanolone a Regenerative Therapy for Alzheimers: FDA-Required Toxicolog

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,637,281.65

Start date of award

15/06/2014

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)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Regenerative Medicine

Research Abstract

DESCRIPTION (provided by applicant): Therapeutics to prevent, delay and treat Alzheimer's disease (AD) remains to be achieved. Currently, over 5 million Americans are diagnosed with AD and the number is projected to increase to 11-16 million within two decades unless therapeutic advances are made. Proposed herein is a regenerative medicine, systems biology approach that targets the regenerative system of the brain while simultaneously activating systems to reduce AD pathology. Allopregnanolone (Allo) is a pleiotropic regenerative therapeutic that promotes neurogenesis and restores cognitive function in both a preclinical AD model and wild type aged mice and reduces pathology in a preclinical AD model. Further Allo promotes regeneration of human neural stem cells. Allo is a neurosteroid endogenous to the brain of low molecular weight and blood brain barrier penetrant with abundant existing safety data in animals and humans. Its mechanisms of neural stem cell proliferation and restoration of cognitive function are well characterized and consistent with well-described neurogenic mechanisms in brain. Allo reduces AD pathology via well-established cholesterol clearance pathways upstream to prevent the generation of Abeta while also decreasing inflammation and increasing myelin generation. Proposed herein is a program of translational IND-enabling toxicological and safety analyses required to advance to a Phase 2 clinical trial of the neurosteroid, allopregnanolone (Allo), for the treatment of persons with MCI due to Alzheimer's disease (AD) or early AD. FDA IND #113,772 is approved for a Phase 1 clinical trial with additional chronic exposure safety analyses required to advance to a Phase 2 clinical trial. Aims proposed within this U01 application specifically address FDA guidance as well as an Aim focused on regulatory documentation and design of the Phase 2 trial. Each specific aim is milestone driven with clearly articulated Go / no-Go decision criteria. Aims I and II will be conducted in two species. Specific Aim I is designed to conduct a nine-month chronic toxicology study to determine the toxicokinetic and safety profiles for intramuscularly administered allopregnanolone. Specific Aim II is designed to conduct a six-month chronic toxicology to determine the toxicokinetic and safety profiles for intramuscularly administered allopregnanolone. Specific Aim III is designed to determine the risk of cerebral micro-hemorrhages after exposure to once per week allopregnanolone in aged mouse model of AD. Specific Aim IV is designed to conduct regulatory assessments and generate documentation for submission to FDA and to generate Phase 2 clinical trial design and plan. A multidisciplinary team of investigators with expertise in Allo systems biology, translational research and clinical trials for AD therapeutics are committed to the project. Outcomes of these analyses will support and advance therapeutic development of Allo to a Phase 2 clinical trial in persons with MCI due to AD and early AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: This project addresses the urgent need to develop therapeutics to prevent, delay and treat Alzheimer's disease (AD). A promising regenerative medicine, Allo, is being developed. Allo activates the brain's own regenerative ability while also reducing the pathology of AD. Studies proposed here are required by the FDA to ensure that Allo is safe to use for extended period of time to generate new neurons, restore cognitive function, reduce AD pathology and to regenerate the connective tracts of the brain.

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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