SMALL MOLECULE THERAPY FOR ALZHEIMERS DISEASE

https://neurodegenerationresearch.eu/survey/small-molecule-therapy-for-alzheimers-disease/

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Country

USA

Title of project or programme

SMALL MOLECULE THERAPY FOR ALZHEIMERS DISEASE

Source of funding information

NIH (NIA)

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€ 952,677.06

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15/05/2016

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1

The project/programme is most relevant to:

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

Research Abstract
? DESCRIPTION (provided by applicant): Alzheimer’s disease [AD] represents a progressive

degenerative illness that affects the brain, resulting in memory impairment. The complex etiology of AD is not fully resolved, although toxic isoforms of amyloid-? (A?) plaques are strongly implicated. Current treatment options are considered to be symptomatic. They are only moderately effective in stabilizing or improving cognitive and functional symptoms. Majority of the research into treatment for Alzheimer's focused on the protein beta amyloid, which is the main component of deposits found in the brain of Alzheimer's sufferers. Unfortunately in the past, many anti-amyloid drugs failed in advanced stages due to safety or efficacy concerns. Thus, there is an unmet need for therapies that halt or substantially slow disease progression. Over the past decade, our continued research has yielded a system to treat AD. Our treatment strategy is based on the observation that A? peptides are in a dynamic equilibrium between the periphery and central nervous system (CNS). Our lead candidate, “”Amytrap””, is composed of a retro-inverso peptide (RIP) that can sequester toxic ?-amyloid peptides A? -40 and A?-42 in the periphery, thereby drawing these toxic peptides out of the CNS. Our research studies have demonstrated the 'proof of principle' of this sequestration effect in vitro and in vivo. The research focused on evaluating the binding capacity of different RI peptides [Amytrap with different peptide sequences] to peptides A ? -40 and A ? -42 in vitro along with its effects on clearance of plaques from the brain in an AD mouse model. The results show that Amytrap is able to reduce A? levels in brain extracts from AD model mice. The reduction in A? levels was associated with improved memory parameters in these mice. Further we have observed suggestive evidence that administration of Amytrap to AD mice at younger age is more effective. This important piece of observation is consistent with the recent findings resulting fro failed/re-emerging human clinical trials. We have further improved the properties of this Amytrap system by linking the RIP to albumin. One of the advantages of the albuminized peptide is the absence of any untoward immune reactions. Recently, we have obtained additional evidence via imaging experiments that Amytrap does not cross the BBB thus reassuring our peripheral sink hypothesis. However, Amytrap warrants further investigation to test its potential as a disease modifying agent. In this phase 2 application, we attempt the next logical decision making point. We propose to conduct expanded studies on efficacy, genetic toxicology and safety pharmacology of the Amytrap molecule. Studies will focus on understanding the properties of Amytrap and translating them to practical applications which will enable us to commercialize Amytrap. Determining the minimum and maximum effective dose of the Amytrap molecule on performance in the “”y”” maze is one of our primary goals that will result in a therapeutic index. We plan to examine the genotoxic potential of Amytrap by standard experiments in vitro and in vivo. We will consequently conduct safety pharmacology studies and evaluate the effect of Amytrap on the CNS, respiratory and cardiac systems over long term. We believe Amytrap is ideally positioned in that it closely resembles its biological target. Further, Amytrap is safe and economical with no side effects. Therefore, we anticipate that Amytrap will be accepted in humans. The proposed commercialization plan includes a strong research team [including a CRO, well verse with IND enabling studies], a comprehensive business plan and commitments from potential strategic partners including Connecticut Innovations Inc [CII] and BioPharma Strategy Advisors, CA. To this effect, CII has already awarded a small grant to RT to fund efforts to bridge the phase 1 with the phase 2 research. The outcome of the proposed phase 2 studies is expected to satisfy mandatory requirements to position Amytrap for a future investigative new drug [IND] filing and subsequent human clinical testing.

Lay Summary

PUBLIC HEALTH RELEVANCE: We have developed and improved the composition of a

proprietary complex detoxification system “”Amytrap”” to treat Alzheimer’s Disease (AD). Our system is based on the observation that A ? peptides (toxic molecules generated in AD) are in a dynamic equilibrium between the periphery and central nervous system (CNS). Amytrap is composed of a retro-inverse (RI) peptide linked to polyethylene glycol and albumin which can sequester toxic amyloid peptides A ? -40 and Aß-42 in the periphery. Addition of albumin appears to enhance the sequestering effect of the RI peptide. We have reproducibly shown that this formulation, which is injected subcutaneously as a gel, is effective in clearing Aß from brai and is non-toxic and non- immunogenic in a mouse model of AD. The proposed phase 2 research attempts to perform genetic toxicology and safety pharmacology studies on Amytrap. The proposed research is aimed to meet the regulatory requirements for an investigative new drug filing (IND). We have put together a strong team of researchers and continued our efforts in establishing partnership with commercial entities to ensure guaranteed progress on commercialization initiatives. At the end of this research period, we expect to generate a potentially new drug candidate to treat AD [pending further clinical testing] and establish a fruitful partnership with a pharmaceutical company to pursue further development.

Further information available at:

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