Small-Molecule Pharmacological Chaperones to Prevent Synuclein Transmission

https://neurodegenerationresearch.eu/survey/small-molecule-pharmacological-chaperones-to-prevent-synuclein-transmission/

Principal Investigators

MCCONLOGUE, LISA C

Institution

J. DAVID GLADSTONE INSTITUTES

Contact information of lead PI
Country

USA

Title of project or programme

Small-Molecule Pharmacological Chaperones to Prevent Synuclein Transmission

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 868,348.62

Start date of award

01/08/2015

Total duration of award in years

1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

synuclein, alpha synuclein, Molecular Chaperones, transmission process, small molecule

Research Abstract

? DESCRIPTION (provided by applicant): Our overall goal is to discover small molecule chaperones targeting ?-synuclein (?Syn) that prevent the prion-like transmission of misfolded

?Syn and can be developed into drugs to treat neurodegenerative diseases such as Parkinson’s (PD), Diffuse Lewy Body, and Alzheimer’s diseases. These drugs will act via a novel mechanism of action by directly interacting with ?Syn to prevent spreading of ?Syn in the brain, with the ultimate goal of reducing disease progression. We envision an innovative strategy by which small molecules bind to and stabilize native or other non-pathogenic states of ?Syn and thereby block pathological events. Most small molecules affecting ?Syn aggregation were found in aggregation assays and interact with aggregation pathway forms of ?Syn. By contrast, we will test compounds that bind to ?Syn native states and affect ?Syn dysfunction more broadly. From a biophysical screen we previously identified 61 compounds that bind to native ?Syn (?Syn-PCs) some of which prevented ?Syn-mediated dysfunctions such as ?Syn aggregation and ?Syn-induced vesicular dysfunction. Based on these promising results, we propose to expand the development of ?Syn-PCs as novel ?Syn chaperone drugs. In this application, we will determine if ?Syn-PCs are a viable strategy to limit ?Syn cell-to-cell transmission and explore the mechanism of action of such active compounds. We will first identify ?Syn-PCs capable of preventing the cell-to-cell transmission of ?Syn and in so doing, identify molecules having potential to be developed into therapeutic drugs. In Aim 1 we will screen the ?Syn-PCs in cellular assays of ?Syn transmission including a FRET-based assay in which transmission is measured as a direct association of donor ?Syn with acceptor ?Syn expressed in different cells. Based on preliminary data we expect to find active compounds. Structure activity relationships will be explored by testing activity of commercially available analogues of active compounds. In Aim 2 we will further identify which steps of transmission are modulated by different ?Syn-PCs. Different compounds will likely affect ?Syn transmission by different mechanisms (e.g., altered cellular levels, location, expulsion, uptake, misfolding) and thus novel mechanisms are likely to be identified using ?Syn-PCs. It will be greatly informative for further therapeutic optimization to explore these novel mechanisms. We will analyze the active ?Syn-PCs to identify which stage in transmission is blocked. Biochemical, microscopic and cell biological techniques will be applied to explore the cellular and extracellular location and state of ?Syn in media and donor and recipient cells. These analyses will elucidate how active ?Syn-PCs modulate the transmission of ?Syn and will shed light on possible assays that would be useful for future development of these molecules into drugs to treat patients. These studies will provide the first evidence for efficacy of ?Syn chaperones in blocking the transmission of a critical protein involved in PD progression and pathology and will provide the foundation for the development of a novel class of drugs for treating ?Syn related neurodegenerative diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: The overall goal of this research project is to find therapeutic drugs for neurodegenerative diseases associated with the protein ?-Synuclein such as Parkinson’s disease, Alzheimer’s disease, and Diffuse Lewy Body disease. Our novel approach is to find small molecules that “”chaperone”” ?-Synuclein to prevent its spreading, aggregation and toxicity in these diseases. This grant proposes to find such small molecules in cellular and animal models of disease as a first step in developing therapeutic drugs based on this approach.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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