HTS to identify small molecules to disrupt abnormal huntingtin interactions in HD

https://neurodegenerationresearch.eu/survey/hts-to-identify-small-molecules-to-disrupt-abnormal-huntingtin-interactions-in-hd/

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Contact information of lead PI
Country

USA

Title of project or programme

HTS to identify small molecules to disrupt abnormal huntingtin interactions in HD

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,782,225.69

Start date of award

01/04/2015

Total duration of award in years

3

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington gene, Huntington Disease, Calmodulin, high throughput screening, small molecule

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) affects one in every 10,000 people in the US, with a current estimate of ~30,000 patients in the US. HD is a

progressive neurodegenerative disease caused by an autosomal dominant mutation coding for a polyglutamine expansion in huntingtin protein. Although the cause of the disease has been identified and genetic tests are available to identify those individuals who carry the mutation and will succumb to the disease, there is currently no therapy to slow or prevent the disease progression, only symptomatic treatments with limited impact. The purpose of the proposed studies is to identify biological probes which can be used for future drug development and eventual testing for their ability to prevent the progressive neurodegeneration in HD. We previously reported in vitro and in vivo proof of concept that disrupting the interaction of mutant huntingtin (mhtt) with calmodulin (CaM) is an outstanding target for treatment in models of HD. We demonstrated that disrupting the binding of mhtt to CaM, with a 46 amino acid peptide, consisting of amino acids 76-121 of CaM, was protective in HEK293 cells transiently expressing a mhtt protein construct, in neuronally differentiated SH- SY5Y cells stably expressing a mhtt protein construct and a transgenic mouse model of HD, R6/2 mice. The goal of the current proposal is to identify selective small molecule inhibitors to disrupt the binding of mhtt to CaM. We have developed and validated a HTS ready, AlphaScreen(r) assay to identify compounds which disrupt the binding of mhtt to CaM. Orthogonal screens will be used to test for selectivity using in vitro assays to test for disruption of the interaction of CaM with other proteins and a cel culture-based assay to evaluate cytotoxicity of the compounds. {Cheminformatic analysis will identify a set of prioritized chemotypes that will be subjected to iterative medicinal chemistry optimization.} Lastly, tertiary screens in a cell culture model of HD will be used to determine whether the chemical probes are neuroprotective against mhtt and disrupt mhtt-CaM interactions in cells. The goal of this project is to identify compounds that disrupt the binding o mhtt to CaM and do so selectively without inhibiting the function of CaM. The top compounds will further protect against both the deleterious effects of mhtt in neuronal cells and the transamidation of mhtt in neurons. The long-term objective of the project, outside of the scope of this proposal is to develop compounds that are protective against the neurodegeneration and other deleterious effects of mhtt in transgenic mouse models of HD and eventually lead to translational clinical testing for HD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Huntington’s disease is a progressive neurodegenerative disease caused by an autosomal dominant mutation coding for a polyglutamine expansion in huntingtin protein. Despite knowing the cause of the disease, there is currently no treatment to prevent the neurodegeneration and death caused by mutant huntingtin protein. The purpose of the proposed studies is to identify biological probes that disrupt the abnormal interaction of mutant huntingtin protein through the use of {1) a high throughput screen, 2) selectivity profiling 3) cluster identification to prioritize chemotypes for iterative medicinal chemistry optimization and 4) tertiary screens. The long-term goal is to produce biological probes for possible future drug development to prevent the progressive neurodegeneration in Huntington’s disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

Database Tags:
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