Selectively inhibited transcription of mutant genes in neurodegenerative disease

https://neurodegenerationresearch.eu/survey/selectively-inhibited-transcription-of-mutant-genes-in-neurodegenerative-disease/

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Contact information of lead PI
Country

USA

Title of project or programme

Selectively inhibited transcription of mutant genes in neurodegenerative disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,072,087.16

Start date of award

30/09/2013

Total duration of award in years

1

The project/programme is most relevant to:

Huntington's disease

Keywords

Neuromuscular Diseases, Huntington Disease, Huntington gene, Neurodegenerative Disorders, Trinucleotide Repeat Expansion

Research Abstract

DESCRIPTION (provided by applicant): Huntington’s Disease (HD) is an inherited disorder that

leads to degeneration of neurons in the brain, mental and physical deterioration, and inevitably, the death of afflicted persons. The disease results from mutational expansion of the number of repeats of the trinucleotide CAG in the huntingtin (htt) gene, resulting in production of a defective Htt protein that forms insoluble aggregates in brain cells. Recent investigations have shown that a transcription elongation complex called Supt4/Supt5h is required for the gene-transcribing enzyme RNA polymerase to proceed through expanded lengths of repeats on DNA templates. When the Supt4h/Supt5h complex is reduced, the expanded repeats of mutated genes present an obstacle that leads to dissociation of the polymerase from DNA-prematurely truncating the mutant transcripts, decreasing production of the defective Htt protein, and enabling neurons that contain the abnormal genes to remain viable. The Supt4h/Supt5h complex is needed also for progression of the polymerase through expansions of multinucleotide repeats associated with other dominantly inherited neurodegenerative and neuromuscular diseases (NDs), suggesting that targeting the Supt4h/Supt5h complex may be a broadly applicable approach for treatment of multiple diseases caused by such expansions; these diseases include, in addition to HD, certain muscular dystrophies and spinocerebellar ataxias. The proposed project will identify potential therapies that interfere with Supt4h/5h complex formation and test the hypothesis that expression of genes containing expanded repeats will be reduced by such therapy, while expression of normal genes remain unaffected. It will develop, test, and validate methods for and suitability of luminescence assays that will be used to screen large chemical libraries and computationally designed peptides for agents that block Supt4h binding to its Supt5h partner (i.e., Supt4h/5h interaction inhibitors; SIIs). Using a procedure that distinguishes between transcription of mutant vs. normal copies of repeat-containing genes, the project will quantify the specificity of SII effects on mutant genes in induced pluripotent stem cells (iPSCs) derived from patients afflicted with HD or other NDs, and will determine the influence of the length of expanded repeats on such specificity. Possible consequences of interference with Supt4h/Supt5h complex formation on transcription of genomic loci external to targeted genes will be assessed by high-throughput RNA sequencing methods (RNA-Seq). The National Center for Advancing Translational Sciences (NCATS) at the NIH will collaborate in screening and medicinal chemistry manipulations aimed at developing promising “”hits”” into therapeutic “”leads””. Collectively, the results of these experiments are expected to: 1) indicate whether interference with Supt4h/5h complex formation can broadly affect production of abnormal gene products in nucleotide repeat disorders, 2) elucidate the quantitative relationship between repeat length and selectivity of Supt4h/Supt5h complex effects, and 3) identify specific agents and/or molecular groups suitable for further development as therapies for these diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: Collectively, the societal burden of Huntington’s Disease and other incurable, inherited neurodegenerative and neuromuscular diseases on afflicted persons, their families, and the health care system is very great. Validation of the hypothesis that these diseases are amenable to a uniform therapeutic approach and confirmation of the Supt4h/5h protein complex as a target for this approach would establish a new paradigm for research on, and treatment of, these horrific diseases.

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:
N/A