Development of SLIC, a methodology for synthetic lethal screening in the CNS

https://neurodegenerationresearch.eu/survey/development-of-slic-a-methodology-for-synthetic-lethal-screening-in-the-cns/

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Country

USA

Title of project or programme

Development of SLIC, a methodology for synthetic lethal screening in the CNS

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,288,495.41

Start date of award

25/09/2013

Total duration of award in years

1

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington gene, Genetic Screening, Neuraxis, screening, Huntington Disease

Research Abstract

DESCRIPTION (provided by applicant): Challenge: New hypotheses in the neurodegenerative disease research field are needed, given the lack of effective therapeutics for most of the major

diseases. In simple model organisms, unbiased, genome-wide genetic screens are used to generate new hypotheses in an unbiased way. Synthetic lethal genetic screens are genetic screens in which a mutation that has no or little toxicity is enhanced by an additional genetic manipulation into a mutation that now does. Thus ‘synthetic lethal’ screens are used to reveal genes and pathways that genetically interact with toxic mutations. Currently it is not feasible to conduct such genetic screens in mice, due to prohibitive cost and numbers of animals needed. We propose to develop a strategy for synthetic lethal in the central nervous system (CNS), which we term SLIC. Impact: The ability to perform unbiased, genome-wide screens in the mouse CNS with our SLIC methodology would allow for the generation of novel hypotheses regarding the etiology of neurodegenerative disease. The potential impact would be myriad new avenues to explore potential therapeutic targets. Once developed, our SLIC methodology could be applied by other researchers to the study of any genetically-induced disease. Approach: We view the lack of cell death found in most mouse models of neurodegenerative disease as a unique opportunity. We propose to conduct synthetic lethal screens in mouse brain, to enhance the toxicity of neurodegenerative disease-associated mutations. SLIC synthetic lethal screens will be conducted by combining the use of i) lentirival shRNA or inducible, barcoded overexpression libraries; ii) stereotaxic CNS injection of these libraries into mouse models of disease and wild-type littermates; iii) incubation of injected libraries, such that shRNAs or overexpressed genes that enhance toxicity will lead to cell death; iv) sequencing and analysis of the remaining shRNAs and barcoded overexpression constructs in all surviving cells, in order to determine which constructs have led to cell death, and thus ‘drop out’ of viral representation. Our work will be conducted along the following specific aims: Aim 1. To develop a methodology that allows for synthetic lethal screens in the mouse central nervous system (CNS); Aim 2. To identify, using the methodology developed in Aim 1, enhancers of Huntingtin toxicity in vivo

Lay Summary
PUBLIC HEALTH RELEVANCE: The ability to perform unbiased genetic screens in model organisms has tremendously advanced our understanding of many cellular processes. Currently, it is not feasible to conduct such screens in higher vertebrates, including mice. The goals of this project are to produce a methodology that allows synthetic lethal screening in the mouse central nervous system, and to apply this methodology to the study of Huntington’s disease.

Further information available at:

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Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

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