Chemical Fingerprinting

https://neurodegenerationresearch.eu/survey/chemical-fingerprinting/

Principal Investigators

MCMURRAY, CYNTHIA THERESE

Institution

UNIVERSITY OF CALIF-LAWRENC BERKELEY LAB

Contact information of lead PI
Country

USA

Title of project or programme

Chemical Fingerprinting

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,530,246.79

Start date of award

01/07/2007

Total duration of award in years

3

The project/programme is most relevant to:

Huntington's disease

Keywords

chemical fingerprinting, Huntington Disease, MSH3 gene, OGG1 gene, oxidation

Research Abstract

DESCRIPTION (provided by applicant): Despite years of intense efforts, there has been no effective therapeutic approach for Huntington’s disease (HD) or other neurodegenerative diseases. The cause of toxicity in HD is poorly understood, and there is no well-defined drug target. Thus, at-risk and affected individuals inexorably progress toward clinical disease, providing an underlying urgency not only to find therapies for the disease, but also to develop

biomarkers to predict the progress of therapeutic outcome. During the last funding period, we have discovered a toxic oxidation cycle in which there is cooperation between the mutant HD protein and the expansion mutation in causing toxicity. Toxicity occurs at four steps, and we have developed promising inhibitors to each one. The most promising compound, XJB-5-131, has a mitochondrial targeted antioxidant properties. Although it is poorly soluble, administration alone alleviates all of the obvious pathological features of disease in an hHdH150Q mouse model for HD. In the renewal, we propose to improve the drug-like properties of XJB-5-131 and use an optimized analog in a “”multi-hit”” therapy in which multiple steps of the toxic oxidation cycles are targeted simultaneously: (1) a tricyclic pyrone for inhibiting the protein aggregates, (2) inhibitors for 8-oxo-G glycosylase, an enzyme that prevents single strand breaks and stops CAG trinucleotide expansion in DNA, and (3) HDAC inhibitors that target MSH2-MSH3, a protein that stabilizes the DNA loops to create expansions. In Aim 1, we propose to co-administer our most successful compound, XJB-5-131, with at least one of the other inhibitors to determine the pharmacology, the optimal route of analog administration, the maximum tolerated dose of each inhibitor combination, and to prioritize in vivo testing according to the best drug-like properties. In Aim 2, we will test the efficacy of multi-hit treatment using simple in vivo endpoints of motor function, cognition, histopathology, and mitochondrial activity to follow therapeutic progression. We will identify which combination of compounds is most effective in offsetting toxicity due to expression of the mutants HD protein. In sum, there are no therapies for HD or methods to speed up the search for therapeutics. New tools and approaches are desperately needed. Our novel discovered compounds and the multi-hit strategy for therapy provide a promising therapeutic approach that warrants further testing to fill these medical gaps.

Lay Summary
PUBLIC HEALTH RELEVANCE: There are no therapies for Huntington’s Disease or methods to speed up the search for therapeutics. At-risk and affected individuals inexorably progressing toward clinical disease provide an underlying urgency, not only to find therapies for the disease, but also to develop biomarkers to predict the progress of therapeutic outcome. We propose a “”multi-hit”” combination therapy to discover inhibitors of HD toxicity. Our novel discovered compounds, the two-hit strategy for therapy, and our new chemical fingerprint tool are rigorous and promising methods, and the use of all in our proposed research will fill these medical gaps.

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