Huntingtons disease biomarkers and therapeutics

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Principal Investigators

DUAN, WENZHEN

Institution

JOHNS HOPKINS UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Huntingtons disease biomarkers and therapeutics

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,862,021.10

Start date of award

30/09/2013

Total duration of award in years

2

The project/programme is most relevant to:

Huntington's disease

Keywords

therapeutic biomarker, Huntington gene, Huntington Disease, Knock-in Mouse, Magnetic Resonance Spectroscopy

Research Abstract
DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a devastating neurodegenerative disorder caused by mutation of the gene huntingtin. No treatment prevented

or slowed disease progression. To develop such a treatment requires objective measures of disease progression. Neuroimaging measures provide unbiased detection of disease progression. The key issues are whether these measures truly reflect the reduction or dysfunction of medium spiny neurons – the nerve cells that selectively die in HD, and whether the neuroimaging measures correlate with other clinical features; more important is whether these measures respond to treatment sensitively and reliably. We propose employing two non-invasive longitudinal neuroimaging measures reflecting different features of the neurons, in vivo structural magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), to determine if these measures provide the sensitive and faithful reflection of the therapeutic efficacy, and how these non-invasive measures correlate with mutant huntingtin-induced functional impairment in the full-length huntingtin knock-in mouse model. In Specific Aim 1, we will validate structural MRI measures as biomarkers and determine their response to neuroprotective treatment in full-length huntingtin knock-in mice. We will determine the correlation between MRI measures and functional impairment in HdhQ250 mice with or without treatment. In Specific Aim 2, we will investigate brain metabolite alterations in parallel with disease progression and determine whether these metabolites respond to neuroprotective treatment by use of magnetic resonance spectroscopy in full-length huntingtin knock-in mice. We hypothesize that alterations of striatal metabolites reflects early neuronal dysfunction and impairment of neuronal circuitry. We will determine if these altered metabolites respond to neuroprotective treatment, and what are the relationships between brain metabolite alterations and functional consequences of mutant huntingtin in the full- length huntingtin knock-in mice. In Specific Aim 3, we will identify clinical candidate small molecule TrkB agonist(s) by using HD cell models and further assess preclinical efficacy, pharmacokinetics, pharmacodynamics, toxicity, as well as mechanisms for promising candidate compound(s) in the full-length huntingtin knock-in mouse model. We will investigate the structure-activity relationship of newly synthesized analogs of 7,8-dihydroxyflavone in HD cell models. The promising candidate compound(s) will be further evaluated for therapeutic efficacy, pharmacokinetics, pharmacodynamics, and toxicity, as well as molecular mechanisms in the full-length huntingtin knock-in mouse model. The ultimate goal of the proposed research is to validate structural MRI and MRS as biomarkers for efficacy trials and prepare therapeutic candidate compounds for HD clinical trials.

Lay Summary
PUBLIC HEALTH RELEVANCE: There is significant unmet medical need for therapies to treat Huntington’s disease (HD) and no reliably validated biomarkers for HD clinical trials. The contribution of the proposed project is expected to validate potential neuroimaging biomarkers and identify candidate compounds for clinical trials. A benefit derived from these studies could be applied directly to clinical trials of HD.

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