Global RNA Interference Therapy for Huntingtons Disease

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Country

USA

Title of project or programme

Global RNA Interference Therapy for Huntingtons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

401376.1468

Start date of award

01/09/2016

Total duration of award in years

1

Keywords

RNA Interference Therapy, Huntington Disease, adeno-associated viral vector, Serotyping, cisterna magna

Research Abstract

Project summary/Abstract Huntington’s disease (HD) is a dominantly-inherited genetic disorder caused by a mutation in the HTT gene (HTT) that leads to widespread degeneration in many regions of the brain and a devastating array of symptoms that include a hyperkinetic movement disorder, gait disturbance, cognitive decline, psychiatric symptoms and metabolic dysfunction. Unfortunately, there is currently no therapy for HD and it always results in death. However, the

emergence of RNA interference (RNAi) as a tool to reduce gene expression has made it possible for our lab and others to develop adeno-associated viral vectors expressing RNAi silencing constructs that target mHTT (AAV-RNAi). We have shown that focal injections of AAV-RNAi into the striatum or the hypothalamus prevent motor and metabolic deficits, respectively, in mouse models of HD. Similarly, my laboratory is currently conducting pre-clinical dosing, biodistribution and safety studies by injecting RNAi constructs in the striatum of rhesus macaques as a prelude to a potential Phase 1 clinical trial. The striatum will be the target of our first AAV-RNAi clinical trial because it is heavily affected in HD, it is a large surgical target and there are clear and robust clinical motor readouts. However, to be clear, the striatum is only one of numerous brain regions affected by the disease. Thus, it is essential that future therapies reduce mHTT expression throughout the entire CNS to provide maximal benefit to the patient. Consequently, the long-term goal of this proposal is to develop a global delivery strategy that effectively reduces mHTT expression in several affected brain regions in HD. This strategy will have a much larger impact on the quality of life of the HD patient. The objective here is to evaluate AAV-PHP.B, a novel AAV9 capsid mutant, as a gene therapy tool to deliver an RNAi construct (mi2.4) to target brain regions affected in HD. Both serotypes will be evaluated using 2 different delivery routes: intra-carotid artery or intra-cisterna magna. The major goals of this proposal are 1) to prepare and characterize AAV-PHP.B-mi2.4, AAV9-mi2.4 and control vectors, 2) to perform pharmacokinetic and biodistribution superiority studies of AAV-PHP.B-mi2.4 and AAV9-mi2.4 in N171-82Q transgenic HD mice to define a dose and delivery route that leads to a significant 40% reduction of mHTT in the cortex and striatum and 3) to perform in vivo efficacy and tolerability studies in 2 different HD mouse models (N171-82Q and BACHD) to establish the minimum effective dose of our lead construct that significantly ameliorates behavioral, neurophysiological and neuropathological deficits germane to each model. These proposed experiments are both significant and innovative because they represent the first steps towards a systemic strategy to attenuate the wide array of devastating symptoms that plague Huntington’s patients.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A