Exosome based therapeutics in Huntingtons disease

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Country

USA

Title of project or programme

Exosome based therapeutics in Huntingtons disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 3,763,689.91

Start date of award

01/08/2013

Total duration of award in years

2

The project/programme is most relevant to:

Huntington's disease

Keywords

exosome, Huntington Disease, Huntington gene, rabies virus glycoprotein G, Antisense Oligonucleotides

Research Abstract

DESCRIPTION (provided by applicant): The goal of this UH2 and UH3 is to study how exosomes can deliver siRNAs across the blood brain barrier to enter neurons and other brain

cells. The immediate target is the mutant huntingtin mRNA. Huntington's disease (HD) is caused by an increase in the CAG trinucleotide repeats to ? 36 in series; it necessitates years in a high level nursing facility because of neurodegeneration first in striatum and cortex and then to other brain structures. HD patients have cognitive impairment, depression and aberrant movements. Most HD patient present by 30 to 40 years of age; a few have a juvenile onset. A rational treatment is to decrease expression of mutant huntingtin mRNA; this therapeutic can be accomplished in HD mouse models by siRNA, antisense oligonucleotides (ASO) and adeno-associated virus (AAV) with shRNAmir directed against huntingtin mRNA. However, delivery remains a pitfall to practical implementation of the therapeutics. siRNA and ASO require long-term infusion. In non-human primates, ASO administered to spinal fluid does not reach the striatum and spread of siRNA is limited in brain. Although promising, AAV-shRNA requires several injections into brain areas and the shRNAmir is unregulated. A gap in HD therapeutics can be filled by microvesicles normally extruded by cells, exosomes. Exosomes with rabies virus glycoprotein (RVG) on their surface can be injected into the blood, cross the blood brain barrier, and enter neurons and glia. RVG-exosomes can carry siRNA cargo. Delivered into the blood circulation, the exosomes deposit siRNA in neurons to engage in RNA interference. Our purpose is to develop exosomes as a therapeutic in HD. The UH2 examines the ability of RVG-exosomes carrying siRNA against huntingtin mRNA to cross the blood brain barrier to enter neurons. Localization in brain and RNAi dependent knock down will be studied. Hyper-functional siRNAs will be sought. Because exosomes are made from cytoplasm of cells, exosome mRNA, miRNA, and implaced siRNA will be identified by deep sequencing. Immune reactivity and immune-neutralization will be studied, since exosomes have potential antigens, like RVG, and will need to be administrated often. The UH3 further establishes exosome-based therapeutics, by study of reversal or prevention of neuropathology and aberrant movement in HD mouse models. Dosing of exosomes will be secured. A team of experts in HD pathogenesis, siRNA development, RNA identification and measurement, RNAi mechanisms and exosome production and brain delivery will carry out the studies. Harnessing exosomes for brain delivery is expected to form a viable therapeutic to reduce expression of mutant huntingtin in patients with HD. Patients with other genetically- based neurodegeneration will benefit.

Lay Summary

PUBLIC HEALTH RELEVANCE: Huntington's disease causes memory and cognitive deficiencies, depression and abnormal movements. It is inherited as autosomal dominant. This means that each child of an affected parent has a 50% chance to inherit Huntington's disease. The disease generally starts between the ages of 30 to 40 in adults, but some patients develop the disease in adolescence. Patients with Huntington's disease often spend 10 years in costly, high level nursing facilities, because of their inability to care for themselves. Between 30,000 and 40,000 patients are affected, with many more at risk. We know the genetic cause of Huntington's disease. We know that application of RNA interference in HD animal models can prevent or ameliorate the disease. RNA interference is a method to attack and destroy mutant huntingtin gene product. However, to date, approaches for RNA interference require direct brain injection or injection into the cerebral spinal fluid. Both are suboptimal and do not have access to diseased brain cells. Exosomes provide an opportunity to treat Huntington's disease by an injection into the vein. Exosomes can be modified to cross from the blood to the brain and transport small RNAs that are used in RNA interference. Exosomes therapeutic in Huntington's disease opens up the possibility to apply them to other brain 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:
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