Nanocarriers Designed to Deliver Nucleic Acids to Brain

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Contact information of lead PI
Country

USA

Title of project or programme

Nanocarriers Designed to Deliver Nucleic Acids to Brain

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,800,125.69

Start date of award

30/09/2015

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

nanocarrier, Manganese, Nucleic Acids, nanoparticle, Green Fluorescent Proteins

Research Abstract

? DESCRIPTION (provided by applicant): Gene therapy of brain diseases is hampered by the requirement for invasive stereotaxic injection into brain, or infusion of therapeutic agents into te intrathecal space. The surgical approach is not optimal for neurodegenerative diseases that

require treatments throughout life. This obstacle has given impetus to the design of a new nose-to-brain delivery system for nucleic acids or drugs that cannot pass the blood-brain-barrier. The overall goal of this project is to refine and test a nanocarrier system consisting of chitosan-based, manganese-containing nanoparticles (mNPs) loaded with therapeutic nucleic acids: small interfering RNA (siRNA) and dsDNA. The experiments are designed to assess the mechanisms and extent to which the nanocarriers transport their payload from the olfactory mucosa to olfactory bulb and other brain regions to suppress marker genes in mouse models of rapid onset Huntington's Disease. Specific Aim 1: Testing optimized nanocarriers loaded with siRNA against a marker gene expressed in transgenic ""green"" mice that constitutively express green fluorescent protein (GFP) in brain neurons. mNPs will be packaged with siRNA directed against GFP. Primary end-points will be a) the extent and time-course of dissemination of mNPs from olfactory bulb to other regions of brain assessed by MRI T1-weighted imaging; b) GFP mRNA and GFP protein expression by comparative quantitiative PCR and Western blot analysis, respectively. Specific Aim 2: Study of gene-silencing in a mouse model of HD. siRNA directed against htt will be loaded into NPs and administered intra-nasally or microinjected directly into striatum in rapid-onset mouse models of Huntington's Disease. Primary-end points will be a) extent and time-course of dissemination of mNPs from olfactory bulb (or from striatum) to other regions of brain assessed by microbore MRI, b) quantitative analysis of htt mRNA expression by quantitative PCR and htt protein expression by Western blot in various brain regions, c) effects on behavior and locomotor activity. Specific Aim 3 a) Iterative optimization of the nanocarrier system in cell cultures expressing a marker gene guided by results from concurrent in vivo experiments in Aim 1 and b) studies of cellular extrusion of exosomes containing mNPs as an hypothesized mechanism for cell-to-cell dissemination. Specific Aim 4: Testing capacity of mNPs to deliver DNA (gene encoding a red fluorescent protein) in vivo. mNPs will be loaded with plasmid dsDNA encoding red fluorescent protein (RFP) and intranasally instilled into normal C57BL6 mice. End-points will be the same as those in Aim 2. Clinical Significance: The ability to dose patients chronically and non-invasively via intra-nasal administration of nanocarriers of gene-silencing agents or other large therapeutic molecules will have a dramatic impact in the therapeutics of brain disorders.

Lay Summary
PUBLIC HEALTH RELEVANCE: The overall goal is to develop a novel drug delivery system to transport large therapeutic molecules (nucleic acids) from nose to brain in a non-invasive, safe and effective manner. The research proposal consists of a series of experiments to test and refine the efficacy of this approach in silencing pathological genes expressed in transgenic mouse models. The ability to dose patients chronically and non-invasively by intra-nasal administration of nanocarriers of gene-silencing agents or other large therapeutic molecules will have a dramatic impact in the therapeutics of brain disorders.

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