ALLELE SPECIFIC GENOME EDITING FOR HUNTINGTON'S DISEASE THERAPY

Published date: Feb. 27, 2018

Technology description

Market Need

Huntington’ s Disease (HD) is an orphan neurodegenerative disease characterized by dementia, declining cognitive function, chorea that gradually spreads to all muscles, hypokinesia, rigidity, and other symptoms of psychomotor decline. Mean onset of symptoms is 30-50 years, however there is a juvenile onset form of HD that occurs under age 20. The progressive neurodegeneration leads to death on average of 20 years after the age of onset. Both forms of the disease are caused by mutations in the huntington (HTT) gene that causes excessive cytosine, adenine, and guanine (CAG) repeats within the gene. Expression of this mutant protein in the brain, particularly in the striatum and motor cortex lead to the functional decline. There is no cure for HD and management of disease over a patient’ s life includes treatment of symptoms with antipsychotics and antidepressants and intensive palliative care.

Technology Overview

The Davidson lab focuses on gene therapy approaches for inherited genetic diseases, specifically rare neurodegenerative diseases for which there are no current treatments. For HD, the group has developed a CRISPR/Cas9-based gene therapy approach to target and induce deletion of the excessive CAG repeats in HTT. The technology takes advantage of the drivers CRISPR/Cas9 specificity, which are the complementarity between the ~20 nucleotide guide RNA sequence and genomic DNA and the protospacer-adjacent motif (PAM) that is juxtaposed to the genomic DNA and guide RNA complementary region. Through prediction of single nuecleotide polymorphism dependent- PAM motifs in the highly mutated regions of HTT, the group was able to create very specific targeting sequences for a CRISPR/Cas9 gene-therapy approach for Huntingon’ s disease. The group has shown that the SNP-specific targeting sequences were allele specific and effective at reducing mutant huntington protein in HD human fibroblasts in vitro. In vivo, using recombinant AAVs to express the sequences in mouse model of huntington’ s disease, the group showed that HTT mRNA levels were specifically reduced in the brain of the treated mice. Additionally, the SNP-based approach to targeting HTT allows for allele-specific deletion, which avoids the loss of normal huntington protein that has been shown to be detrimental. Compared to other technologies, such as RNAi, which are also being studied for HD treatment, this is a significant distinction and advantage of this technology.

Advantages

• Treats cause of HD
• SNP-based targeting allows for allele-specific deletion of mutant gene

Institution

The Children's Hospital of Philadelphia

Inventors

Beverly Davidson
CSSO and Center Director
Path
Alejandro Mas Monteys
Instructor
Pathology and Laboratory Medicine
Shauna Ebanks

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com