Epigenetic Editing of Mutant C9orf72

https://www.neurodegenerationresearch.eu/survey/epigenetic-editing-of-mutant-c9orf72/

Principal Investigators

LEE, EDWARD BYUNG-HA

Institution

UNIVERSITY OF PENNSYLVANIA

Contact information of lead PI
Country

USA

Title of project or programme

Epigenetic Editing of Mutant C9orf72

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,834,862.39

Start date of award

15/02/2016

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias|Motor neurone diseases

Keywords

C9orf72, frontotemporal degeneration, Epigenetic Process, Dipeptides, Methylation

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration (FTD) are two related neurodegenerative diseases which share overlapping clinical, pathologic and genetic features. The ALS/FTD spectrum of diseases is uniformly fatal, and there is neither treatment nor cure. The endogenous mechanisms which exacerbate or mitigate disease progression in these diseases are not clearly understood.

However, a mutation within the C9orf72 gene has been discovered as the most common genetic cause of ALS/FTD. The mutation consists of a hexanucleotide repeat expansion which has been proposed to lead to the accumulation of toxic RNA and protein species. C9orf72 mutations are also associated with C9orf72 promoter hypermethylation in a subset of mutation carriers. Promoter hypermethylation appears to protect against many of the molecular aberrations associated with the C9orf72 mutation including DNA repeat instability, toxic RNA accumulation, dipeptide repeat protein accumulation and cellular vulnerability to stress. C9orf72 methylation also predicts prolonged disease duration, maintenance of grey matter, and preservation of memory function in FTD patients with the C9orf72 mutation. Based on these findings, the hypothesis of this proposal is that epigenetic editing of mutant C9orf72 can modulate disease pathogenesis. To test this hypothesis, I have developed a novel method of introducing or removing CpG methylation within the endogenous genome, and propose three specific aims to (1) determine the molecular mechanisms and specificity of targeted epigenetic editing, (2) introduce C9orf72 hypermethylation in patient-derived iPS cells as a proof-of-concept study to show that epigenetic targeting can be therapeutic, and (3) develop improved models of disease by demethylating the C9orf72 promoter in iPS cells with large C9orf72 repeat expansions. These studies will bring to reality the possibility of epigenetic editing as a means of modulating neurodegenerative disease phenotypes, and will highlight the utility of a novel epigenetic editing technique that is broadly applicable across many disciplines.

Lay Summary
PUBLIC HEALTH RELEVANCE A mutation in the C9orf72 gene is the most common heritable cause of amyotrophic lateral sclerosis and frontotemporal degeneration, and epigenetic silencing of this mutation appears to be protective. This project will study a novel method of editing the epigenetic status of C9orf72 in order to protect cells from the deleterious effects of the mutation.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias, Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A