C9orf72 repeat expansion in FTD/ALS – from mechanisms to therapeutic approaches

https://neurodegenerationresearch.eu/survey/c9orf72-repeat-expansion-in-ftdals-from-mechanisms-to-therapeutic-approaches/

Principal Investigators
Institution
Contact information of lead PI
Country

European Commission

Title of project or programme

C9orf72 repeat expansion in FTD/ALS - from mechanisms to therapeutic approaches

Source of funding information

European Commission FP7-Seventh Framework Programme

Total sum awarded (Euro)

€ 1,991,000

Start date of award

01/05/2014

Total duration of award in years

5.0

The project/programme is most relevant to:

Motor neurone diseases|Alzheimer's disease & other dementias

Keywords

Research Abstract

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are fatal neurodegenerative diseases with overlapping genetics and pathology. The most common known cause is expansion of a GGGGCC repeat in the first intron of the gene C9orf72. I discovered that the repeat region is translated in all three reading frames into aggregating dipeptide-repeat (DPR) proteins despite its intronic localization and lack of an ATG start codon. DPR aggregates outnumber the previously identified TDP-43 inclusions in the hippocampus, cortex and cerebellum. Some patients exclusively show DPR pathology, strongly suggesting DPR production is a key pathomechanism in C9orf72 mutation carriers. However, we know next to nothing about the mechanisms of translation, toxicity, aggregation and clearance of DPR proteins. With this grant I will characterize this unusual pathomechanism in detail.

First, I will generate monoclonal antibodies for a comprehensive analysis of all DPR species to determine the best pathological correlate of disease progression. Insights from patients will drive mechanistic studies and will help to identify therapeutic targets within the DPR cascade. Second, I will develop cell culture models to identify the molecular pathways that determine the expression, toxicity and aggregation of DPR proteins. These models will be used to identify drugs that block all steps of the DPR cascade in pilot screens. Third, I will create transgenic mouse models expressing DPR proteins to rigorously validate the DPR hypothesis by comparing pathology and clinical symptoms of transgenic mice and human C9orf72 patients. Finally, these mouse models will be used to test promising compounds identified in cellular models in prevention and treatment trials. Moreover, I will analyse whether passive immunization with the newly developed monoclonal antibodies allows clearance of DPR proteins from the brain as it has been shown for other intracellular aggregating proteins such as a-synuclein.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
European Commission

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

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