Wellcome Trust/MRC Strategic Award: The role of RNA-processing proteins in neurodegeneration

https://neurodegenerationresearch.eu/survey/wellcome-trustmrc-strategic-award-the-role-of-rna-processing-proteins-in-neurodegeneration/

Title of project or programme

Wellcome Trust/MRC Strategic Award: The role of RNA-processing proteins in neurodegeneration

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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Address of institution of lead PI

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Country

- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

5668338.56

Start date of award

01-01-2010

Total duration of award in months

60

The project/programme is most relevant to

- Alzheimer’s disease and other dementias
- Motor neurone diseases

Keywords

Recent genetic and pathological discoveries have placed the RNA-processing proteins, TDP-43 and FUS, centre stage in the pathogenesis of ALS and FTLD-U. Here we present evidence that FUS and TDP-43 mislocalise and aggregate in FTLD-U patients with PGRN mutations. Aberrant processing of transcripts may cause neurodegenration due to a loss of function; however, these proteins also aggregate in affected neurons and may cause a toxic gain in function. The main aim of this proposal is to generate cellular and animal models to determine which mechanism is predominant (or whether both are necessary) and identify the events that initiate neurodegeneration. We will:

1) Generate and characterise cellular models of PGRN, DP-43 and FUS mediated neurodegeneration.

2) Generate and characterise zebrafish and mouse models of PGRN, TDP-43 and FUS mediated neurodegeneration.

3) Identify the physiological DNA and RNA binding targets of TDP-43 and FUS in cells and animal tissues.

4) Define the transcriptional and proteomic signatures for loss and/or gain of function for PGRN, TDP-43 and FUS in cellular and animal models.

5) Interrogate FTLD and ALS nervous tissues for loss and/or gain of function transcriptomic or proteomic signatures and compare these to other neurodegenerative disorders

6) Identify the major sites of in vivo phosphorylation of TDP-43 and FUS, the kinases responsible and the functional consequences of these post translational modifications.

Lay Summary