New mouse models for tackling motor neuron disease and other neurodegenerative disorders

https://neurodegenerationresearch.eu/survey/title-of-pinew-mouse-models-for-tackling-motor-neuron-disease-and-other-neurodegenerative-disorders/

Title of project or programme

Title of PI	New mouse models for tackling motor neuron disease and other neurodegenerative disorders

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
Professor	Elizabeth	Fisher	University College London	UK

Address of institution of lead PI

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- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

1181335.08

Start date of award

01-08-2009

Total duration of award in months

48

The project/programme is most relevant to

- Motor neurone diseases

Keywords

Research abstract in English

Amyotrophic lateral sclerosis (ALS) is mostly (~80%) sporadic but familial forms (FALS, ~20%) are known. The SOD1 gene is the most common causative gene for FALS, and recently rare mutations have been identified in the TDP43 gene. This is of interest because TDP43 is the major ubiquitinated

protein in inclusions in both sporadic and familial ALS although not SOD1 related ALS.

We are requesting funding for one postdoc and one technician (minimum staffing to make this application realistic) to create two novel mouse strains modelling amyotrophic lateral sclerosis (ALS) with the SOD1 human genomic coding region knocked in, and two novel strains with a human TDP43 cDNA knocked in. These mouse strains are essential for understanding ALS because: if the knock in mice have a mid-life disease, this would arise from mutation, not from overexpression of the transgene array, which is known to have an effect in existing SOD1 transgenics; the model is physiologically more relevant than existing transgenics, giving us a better understanding of pathology and a better model for conventional and gene therapeutics including siRNA and lentiviruses; this model also gives us a better knowledge of the protein interactions that occur in ALS because it is biochemically more relevant to the human disease; this model helps address the biophysics/biochemistry of mutant:wildtype dimers and enzyme function, in a variety of primary cell lines, including embryonic stem cells and motor neurons; a mouse with late onset disease will direct us to biomarkers, desperately needed by ALS clinicians. Critically, we will make Cre-conditional knock in mice in which the mutation can be turned off in any tissues thus informing us, for example, about motor neuron glia interactions as we already know SOD1 induced motor neuron death is not cell autonomous and therefore glia and other cells may be targets for therapy. We wish to make knock in mice for both mutant SOD1 and TDP43, because although mutations in these genes may feed into a final common pathway, the lack of TDP43 pathology in SOD1 mutant ALS clearly shows the genes have different initial effects.

A critical feature of this award is that we will make the mice freely available immediately, via the European Mutant Mouse Archive and the Jackson Laboratory, for distribution to all interested laboratories.

Lay summary
In which category does this research fall?

- Basic research