New humanised mouse models for dissecting the pathobiology of disease, using FUS-ALS as a paradigm

https://neurodegenerationresearch.eu/survey/new-humanised-mouse-models-for-dissecting-the-pathobiology-of-disease-using-fus-als-as-a-paradigm/

Principal Investigators

Professor E Fisher

Institution

University College London

Contact information of lead PI
Country

United Kingdom

Title of project or programme

New humanised mouse models for dissecting the pathobiology of disease, using FUS-ALS as a paradigm

Source of funding information

MRC

Total sum awarded (Euro)

€ 1,080,439

Start date of award

31/08/2014

Total duration of award in years

3.0

The project/programme is most relevant to:

Motor neurone diseases

Keywords
Research Abstract
Many genes, including the well-known genes FUS, TDP43, SOD1 that are causative for the neurodegenerative disease amyotrophic lateral sclerosis (ALS) are dosage-sensitive. ALS is an

incurable and essentially untreatable disease that leads to paralysis and death through the progressive loss of motor neurons. ALS is generally a mid-life disorder but patients as young as 11 years of age (with FUS mutations) have been described. Most familial forms of ALS arise from dominant mutations and are modelled in mice by overexpression of the human mutant transgene. However, phenotypes arise in transgenic mice from overexpression per se, rather than from the effects of the mutation. To create more sophisticated models that overcome issues of dosage-sensitivity and express the biochemically correct human protein at physiological levels, we have developed a new technology that is straight-forward and should be useable by standard-gene targeting laboratories. We have created 'genomically humanised' animals in which the mouse gene is entirely replaced by the human genomic locus. These mice express the mutant protein at physiological levels. We are now applying for funding to achieve two goals, (1) to develop our genomic humanisation technology to create conditional mutants and, (2) to characterise our new mouse lines and shed light on the biology and pathology of our paradigm, FUS, in health and in neurodegeneration. By the end of this program of research we will have informative new FUS models for the community, and a better understanding of how mutant FUS causes neurons to die. The normal biology of FUS is not well understood and FUS mutations can be particularly aggressive, often causing ALS in young teenagers and adults, for as yet entirely unknown reasons. FUS is also involved in other neurological diseases, and is an important target for our attention. This technology is applicable to any organism for which ES cells exist, not just mice.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A