Home Office

NON-TECHNICAL SUMMARY

The molecular pathology of axonal degeneration.

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.

Key words

Axon, Lysosome, Paralysis

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

We study inherited conditions that cause progressive leg paralysis, sometimes accompanied by other medical problems. The underlying problem is one of death of axons, the part of nerve cells that connects to other nerve cells over long distances. These conditions are currently untreatable, so it is critical that we understand the problems inside cells that cause them, as this may suggest treatment options. In this project, we examine whether and how problems with a single vital component within nerve cells, called the lysosome, are linked to causing unhealthy axons. Lysosomes are a recycling and disposal centre within the cells. We also aim to determine whether treatments to improve how lysosomes work might be used to keep the axons in good health.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

What are the potential benefits that will derive from this project?

The project will increase our knowledge of the mechanisms that cause death of axons. This is seen in many common human health conditions affecting the brain, such as in Alzheimer dementia, so it is very important that we understand how it is caused.
The project will also increase our knowledge of the factors in cells that are needed to keep lysosomes functioning properly.
If we are successful in identifying treatments that improve lysosomal and axonal function, in the longer term this may lead to treatments for more common brain disorders.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

Up to 2000 adult mice and up to 3700 foetal mice (which are used to make nerve cells in a dish and to safeguard important mouse strains by freezing embryos), over 5 years.

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

We use mice that mimic the human disease. Thus the mice develop a walking problem, but this is very mild and not obvious on normal daily care of the mice. We measure walking abnormalities by generally painless tests, such as running on a treadmill. At the end of the experiments, the animals will be killed by a humane method, and we may also use cells and tissues from mice that have been killed in our experiments to understand lysosome function and how this causes the disease.

Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

We use genetically engineered mice that are an excellent model of the human disease, in that they develop very similar neurological features to patients with who have diseases that cause death of axons. This means that we can use cells and tissues from the mice to try to understand the causes of the conditions. It would be impossible to obtain equivalent material from human patients, and lower model organisms, such as zebrafish and flies, do not accurately represent the mammalian nervous system.

Reduction

Explain how you will assure the use of minimum numbers of animals.

We use good breeding techniques to minimise the number of animals obtained.

Where possible we use statistical modelling to estimate the correct number of animals to use in experiments.

We carry out pilot experiments using cells in a dish before using tissues from animals. We also maximise the number of experiments carried out on any set of animal tissues, and use the minimum number of experiments to achieve robust and reproducible results.

Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

The mouse models that we use to study axon death develop a mild, late onset gait abnormality that does not interfere with the animal's general activities. Thus distress to the animals is likely to be very small. We will monitor animals to check that more significant gait abnormalities have not developed. For analysing mouse gait, we use a digital motorised treadmill device that generates multiple quantified gait data while the animals walk or run, thus maximising the amount of information obtained from each animal and minimising the number of individual tests required. As the data are very precise, this also means that fewer mice are needed to obtain statistically significant results.