Home Office

NON-TECHNICAL SUMMARY

Mechanisms of axon and synapse loss

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.
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants.

Key words

axon, synapse, degeneration, Alzheimer’s, neuroprotection

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?

Axons are the long wires that conduct electrical signals around our brains and bodies from one nerve cell to another, or from our nerves to our muscles. Their extreme length makes axons vulnerable in disease. Our research group has pioneered the understanding of a widespread, and preventable mechanism of axon degeneration involving specific proteins in our nerve cells. Consequently, four proteins are known to regulate axon survival and degeneration, there is clear evidence that this mechanism is relevant to human diseases. The Pharma industry is now targetting this pathway for drug development. The next steps that we address here are (a) to determine how the proteins regulating this pathway interact with one another as a clue for how to block the pathway with drugs (b) to identify the human diseases in which it will be most effective to block this pathway, partly using animal models (c) to find ways to preserve synapses at the ends of axons, which are essential for sending chemical signals to the next cell.

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 axon degeneration pathway we study regulates axon survival in many diseases. These include nerve disorders arising from diabetes and cancer chemotherapy, Parkinson's disease, glaucoma, multiple sclerosis, traumatic brain injury, motor neuron disease, and stroke. It also seems to cause some types of abnormal pain and some cases of stillbirth in humans. A role in nerve disorders, associated with HIV, polio and other viruses, and in Alzheimer's disease (the most common cause of dementia) is also possible. Any or all of these disorders could be alleviated if we could develop drugs to block this pathway. In a new Alzheimer's (3Rs) model we have developed, we find synapse loss similar to that in patient brains and have made substantial progress in understanding and preventing the mechanism. By extending this research further we can open new ways to target Alzheimer's disease and we can extend this 3Rs method to studies of other neurodegenerative 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 27,000 mice or rats (over 95% mice) and 4,000 zebrafish may be used during the five year period. The vast majority of our work (ca. 80% of the rodents and all the zebrafish) involves the breeding and brief maintenance of genetically altered animals with no adverse effects. This is essential to produce sufficient nervous system tissue for the 3Rs methods we are increasingly using, such as cell culture and working with zebrafish embryos before they are able to feed freely. Up to 1,000 mice may develop disease signs so we can study how to alleviate disease.

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?

Most animals will be completely healthy during life and will be humanely killed by an authorised method to obtain nerve tissue for cell culture. Similarly, zebrafish will be only used for breeding to obtain embryos for nonregulated procedures before reaching free-feeding stage. Animals with signs of disease may develop varying degrees of tremor or hindlimb weakness, ranging from unimpaired mobility around the cage to early stages of hindlimb paralysis. Food and water will provided in accessible form and if limb weakness becomes more advanced, and animals will be killed by an authorised humane method before losing any significant forelimb function. Other interventions include lesioning a leg nerve in mouse or rat on one side to study nerve degeneration. This is carried with the highest surgical and aseptic standards under general anaesthesia, alleviated with analgaesic for pain relief and closely monitored subsequently. Animals recover quickly and movement around the home cage is near normal. A small minority of animals will be used in studies of transient pain, but this has no lasting effect, and some may be used for dosing with potentially neuroprotective drugs to determine their efficacy.

Replacement

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

Many replacement methods are used in our work. We do a lot of work in primary neuronal cultures to study nerve injury, and we culture slices of brain tissue to study Alzheimer’s disease mechanisms. We work with nerves removed from humanely killed animals in a dish and zebrafish embryos to study events within nerve cells. However, to understand the functioning and degeneration of the human nervous system we ultimately have to confirm findings from this work in a live mammal. Mice are the species for which genetic methods and analysis are most advanced so this is why they are chosen over other species here. Rats are sometimes needed for a greater supply of tissue or for confirmation of findings in a second mammalian species.

Reduction

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

The best way to reduce numbers is to do well-designed experiments limited to novel and important questions. Our research group has the highest standards of research with a strong track record of publications and we are world-leading in the fields of axon degeneration and synapse loss. Careful experimental planning is also key, so we reduce the numbers needed by minimising variability within groups, correct use of controls, and the use of pilot experiments and power analysis for new methods where the outcome is unpredictable.

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.

We refine our use of animals by using the highest standards of aseptic surgery to avoid infections (we have never had a single case of infection), by maintaining strains of animals as carriers rather than breeding parents affected by a disease, and by applying strict humane endpoints. We house animals in groups wherever possible and we use pre- and post-operative analgesia. Our pain studies are refined wherever possible by giving animals a choice between a potentially painful experience and a non-painful one and monitoring their choice.