NON-TECHNICAL SUMMARY

Mechanisms to medicines in neurodegenerative diseases

Project duration

5 years 0 months

Project purpose

- (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

Neurodegenerative diseases, Neuroprotection, Alzheimer's disease, Dementia

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 is the aim of this project?
Neurodegenerative disorders, such as Alzheimer’s and Parkinson’s diseases, are a group of fatal conditions that cause loss of memory and mental ability due to death of brain cells (dementia). Currently, no treatments exist for these conditions and they pose an ever-increasing burden on families, society and healthcare systems worldwide.

We recently discovered a key process that causes brain cell death in mice with these diseases, which we have targeted with drugs, curing disease and preventing death of brain cells in mice. The same process is affected in human neurodegenerative diseases. We have recently discovered a safe, licensed drug which is ready for clinical trials in dementia patients. We now aim to increase our knowledge and understanding of the way that this drug works and identify more pathways and compounds which protect brain cells and drive the discovery of new, safe, treatments for dementia and neurogenerative disease.

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 impact of possible new treatments for neurodegeneration on the lives of individual patients and carers, on healthcare services and on the global economy in the context of an ageing population, is potentially enormous. Finding drugs to target the processes underlying brain cell death will benefit learning and memory, as well as protecting brain cells from dying. By testing drugs that are already safe to use in humans we hope to be able to transfer these to clinical trials more quickly. In the long term, even modest delays in disease onset or progression could have significant impact worldwide.

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?

Mice, both wild type and genetically modified. To date we have used ~16,000 mice in 5 years. However, where possible we replace mice with cellular models (see 3Rs section). We would nonetheless expect to use up to ~25,000 mice over 5 years for developing new models of dementia and testing of potential treatments.

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?

The mice will be models of neurodegeneration i.e. dementia models such as Alzheimer’s and prion, and frontotemporal dementia models. Some of the animals will never show any visible signs of distress
however some will show signs of disease such as movement and behavioural changes. Those that do will be carefully monitored by daily observation and examination of weight to limit both the length of the experiment and any suffering caused. Where needed, these animals will be given pain relief and easier access to food and water. In most cases, mice will not exceed a level of moderate severity. Mice will be humanely killed as soon as relevant clinical signs of disease are seen or other suffering. When new compounds are used, adverse effects may result, these will be rigorously monitored and appropriate action taken. Occasionally mice will undergo surgery, to deliver substances to specific brain regions. During these 30 min-1 hour surgeries, very small holes will be drilled into the skull and an ultrafine needle used to deliver these substances. Mice recover quickly and will be given pain relief and post-operative care. At the end of each study, animals will be humanely killed and tissue taken for analysis and further studies.

**Replacement**

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

Neurodegenerative diseases are fatal disorders for which there is no cure. To understand what causes them and how to treat them, studying them in experimental models is essential. Mice provide an excellent model for many aspects of human disease. They are ideal for studying prion diseases as they reproduce all key features of the disease: long incubation times, loss of normal brain function and cell death. They also model brain cell loss and changes in movement and mental ability of other neurodegenerative disorders such as Alzheimer's disease. By using mice with prion disease, we have discovered new reasons for brain cell loss and new treatment targets for dementia. We now need to understand the role of this in neurodegeneration more broadly, and the effects of modifying it for new treatments for dementia. The complexity of the brain, and the need to use systems that can accurately model neurodegenerative diseases, means that there is no substitute for animal experimentation. Insufficient information exists to generate accurate computer models that can predict the complex responses of brain tissues. Whilst many studies can and will be done in cells in culture, intact brain with its full complement of brain cells is the only system in which mechanisms can be fully tested and therapies be accurately evaluated. Mice share many similarities in brain structure with higher mammals, including humans and many of the mechanisms, processes and pathways are identical to those in humans. Further, the availability of genetically modified animals with particular genes knockouts or overexpression make them useful tools for testing the importance of particular process in neurodegeneration. Thus, these species are the most appropriate for testing basic aims, which can be relevant to human health.

However, where possible we will use cell culture for testing new drugs for the treatment of neurodegenerative disease. However, the clinical validity of these and their relevance to human disease ultimately requires validation in mouse models.

**Reduction**

**Explain how you will assure the use of minimum numbers of animals.**
We will use the minimum number of mice needed in all experiments for reproducible results and statistical validity in line with the ARRIVE guidelines www.nc3rs.org.uk/ARRIVE. We will use published protocols to guide statistical validity in all our experiments. We will also use the PREPARE guidelines (https://norecopa.no/prepare) and the NC3RS Experimental design assistant (https://www.nc3rs.org.uk/experimental-design-assistant-eda) to help plan and design our future experiments. We are committed to keeping the numbers of mice to a minimum by maximising the use of each experimental animal (see below), e.g. taking tissues from different halves or parts of the brain for biochemistry and histology after behavioural assessment and neurophysiology, therefore maximising readouts from any one animal. For genetically altered animals, where suitable lines already exist, animals will be obtained from the relevant supplier. Otherwise, we will have the required lines made by reputable companies.

We will ensure high standards of animal care, welfare and utilize the most appropriate breeding methods. Colony sizes are monitored and adjusted within a formal forecasting system to meet the requirements of the research programme. Breeding colonies are always kept to their minimum size so as not to over-produce and to avoid wastage.

Where it is possible to avoid using animals by growing primary cell cultures from their brains, we will use this approach. A single new-born pup can provide enough cells for whole experiments that we will use wherever this is a feasible alternative.

**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.*

Non-mammalian species (such as flies and worms) do not share sufficient commonalities in their central nervous system to make them appropriate models for human disease. Rats and mice share many similarities in brain structure and processes with higher vertebrates. Furthermore, the availability of transgenic animals with particular genes knocked out or overexpressed make them useful tools for testing the importance of particular genes in neurodegeneration model systems. Thus, these species are the most appropriate for testing basic hypotheses, which can be relevant to human health before moving into higher vertebrate species.

For genetically altered animals not infected with prions, the most invasive procedure is likely to be intracerebral injection with modified viruses or other substances. This is carried out under general anaesthesia and the animals are given pain relief for the craniotomy scar. Most animals will receive one set of bilateral injections and not more than two, on separate occasions, not less than one week apart.

Administration of other substances will be given with due care and pain relief if appropriate as well as staged dosing, in general not more than daily dosing.

To study cooling as a method of neuroprotection we will use a technique that mimics the biochemical changes that occur during hibernation in small mammals and in which the mice return to normal temperature within a few hours with no lasting signs of stress.