



Home Office

## NON-TECHNICAL SUMMARY

# Microglial targets in brain pathology and ageing

### 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

Brain disease, Alzheimer's disease, Ageing

## 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?

Nerve cells (neurons) and their connections (synapses) can be 'eaten' by another type of brain cell, called microglia. The aims of this project are: (1) to find out whether the loss of nerve cells and their connections during ageing and brain diseases, such as Alzheimer's disease, is due to microglia eating

these synapses and neurons, and (2) to find drugs or potential treatments that prevent loss of brain nerve cells and their connections by blocking microglia from eating them.

**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?**

Alzheimer's disease is now the most common cause of death in the UK, and there are no treatments that affect progression of the disease, so that if we found a treatment, it would be beneficial. Reduced ability to learn and remember is very common with age, and there is no known treatment, so if we found a treatment, it would be beneficial. By blocking the microglial cells from eating nerve cells and their connections during brain ageing or Alzheimer's disease, we may be able to prevent brain ageing and Alzheimer's disease. We have found that this is true in: brain cell culture and some simple mouse models of Alzheimer's disease and ageing. In this project we aim to: i) test whether blocking the eating of neurons is beneficial in animal models of brain disease, and ii) test how best to block this eating in order to protect the brain from ageing and disease. The animal models of brain disease used in this project will be more realistic than those previously used because, for example, we will be using the human disease-causing proteins expressed in the mice.

**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?**

Rats 1100  
Mice 2440  
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?**

Most of the mice and rats will be killed within a few days of birth, causing transient pain. Brains from these animals will be used to isolate brain cells, which we will use to investigate how to prevent microglia eating nerve cells. Some experiments will involve injecting into mouse brains substances that cause loss of nerve cells, so that we can investigate how this happens and how we can prevent it. The mice will be anaesthetised when we do this, but when regaining consciousness or as a result of the substances injected they may feel mild or moderate signs such as humans have during a cold or flu, including clinical signs such as fever, disrupted sleep, reduced activity and loss of appetite. A mouse model of Alzheimer's disease will cause impaired memory and wobbly gait, but we will use a welfare-

monitoring system to make sure that mice do not develop marked disability/disease before being humanely killed. All animals will be humanely killed at the end of the experiments, and tissues from the animals will subsequently be analysed.

## Replacement

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

We have already done extensive experiments that do not use live animals. However, it is now essential to determine whether the eating of nerve cells by microglia occurs in realistic animal models of human disease, and how we can prevent this to protect the brain. We have previously used some animal disease models in which blocking the eating of nerve cells by microglia was strongly protective, but these models have limited application to human disease, and only have relevance to some diseases but not others. We now need to use more realistic animal models of human disease in order to test whether we can protect the brain, otherwise we will not be able to progress towards developing treatments for human disease.

## Reduction

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

The lowest numbers of animals will be used consistent with obtaining a reasonable estimate of experimental variability to test for meaningful results between treatment groups. Previous results indicate that about 8 animals per treatment group is the minimum required to achieve statistical significance. We will only test drugs in animals, when we know they work with isolated brain cells. All the experiments will have appropriate controls, and will be designed to reduce variation and bias, and increase the reproducibility of the results obtained.

## 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.**

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We will only be using rats and mice for this research (the lowest vertebrates for which there are established models of brain disease relevant to human disease). We will be using the minimum numbers of animals compatible with obtaining statistically significant results. And we will be using disease models with the minimum suffering compatible with relevance to human brain disease. When using models of Alzheimer's disease, we will use a welfare-monitoring system to make sure that mice do not develop marked disability/disease, and that any suffering is minimised by pain relief. Animals that have been transported (which can be stressful) will be acclimatised (destressed) for at least three days before being used for experiments. The housing environment of the mice and rats will be enriched with bedding, play, nesting and gnawing materials.

