

G. Non-Technical Summary (NTS)

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed programme of work clearly using non-technical terms which can be understood by a lay reader. You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary will render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at www.gov.uk/research-and-testing-using-animals).

Word limit; 1000 words

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|----------------------------------|---|
| Project Title | Understanding the role of inflammation in dementia |
| Key Words | Alzheimer's disease, Dementia, inflammation, co-morbidity |
| Expected duration of the project | 5 year(s) 0 months |

Purpose of the project (as in ASPA section 5C(3))

Purpose

Yes (a) basic research;

(b) translational or applied research with one of the following aims:

Yes (i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants;

No (ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants;

No (iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.

(c) development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the aims mentioned in paragraph (b);

No

(d) protection of the natural environment in the interests of the health or welfare of man or animals;

No

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No (e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work;

No (f) higher education or training for the acquisition, maintenance or improvement of vocational skills;

No (g) forensic inquiries.

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):

Here we aim to understand how inflammation contributes to dementia such as that seen in Alzheimer's disease (AD). AD is the most common cause of dementia in the elderly with over 850,000 people in the UK being affected, and this is expected to double within 20 years. Therefore, AD represents a significant medical problem, especially as there is currently no cure and no way to slow progression of the disease. There is therefore an urgent need to understand in more detail the underlying mechanisms that contribute to AD, so that new treatments can be developed. The inflammatory response is how our immune system reacts to a stress or danger. Danger signals that are released in the brain of someone with Alzheimer's disease (AD) alert the immune system and inflammation then occurs. It is thought that this inflammation is bad for the brain and contributes to the problems seen in AD such as memory loss. However, we do not fully know how this inflammation happens and we aim here to find out. We also want to try to find ways to stop this inflammation from happening or from stopping it doing damage.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?

The overall benefit of this programme of work is related to new knowledge about how inflammation affects dementia and AD. In defining this contribution we hope to be able to identify and test new ways to help these conditions.

What types and approximate numbers of animals do you expect to use and over what period of time?

Mice (5000) and rats (1500) will be used over a 5 year period.

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

Mice and rats will be used as there are several available mouse and rat models of AD. These animals appear normal and healthy but develop problems in their memory over time. Disease progression will be monitored over several months by mainly studying pathology and behaviour. Pathology will be tested post-mortem, but we will also scan the brain, which will allow the progression of AD to be studied in the same animal over a long period of time,

reducing animal numbers. We will test the animals' memory using a series of well-described tasks that are not harmful to the animals. Much of our analysis will be carried out post-mortem on tissue from animals that undergo no treatment and therefore no adverse effects are expected in these animals. Where there is treatment or an intervention (induction of inflammation) some mild changes may be observed e.g. induced infection may cause a fever and sickness-like behaviour in the animals, but these effects are transient. One of the behavioural tests (Morris Water-Maze) involves placing the mice in a pool of water, which may induce mild stress, but steps will be taken to reduce stress. Animal welfare will be continually monitored and any issues will be discussed with the named veterinary officer. No serious adverse effects are expected and we are very well aware of minor adverse effects that may be seen, and have taken great efforts to reduce them.

Application of the 3Rs

Replacement

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

Replacement

Mice and rats will be used in this project. Studying the mechanisms involved in dementia and AD is extremely complex and involves understanding the interactions between different systems in the body (e.g. nervous, immune, and vascular). It is very difficult to mimic such complex interactions *ex vivo*, and whole animal *in vivo* experimentation is therefore vital in order to obtain a greater understanding. In addition to the pathological changes in the brains of AD patients, the disease is characterised by problems in learning and memory, and as such this behaviour is very difficult to model *in vitro*.

The proposed studies could not be undertaken in lower species because they do not show such similarities to humans (e.g. do not have some of the immune molecules), and *in vitro* experiments do not allow the study of interactions between different body systems (i.e. immune and vascular), which are critical for this project. Thus, the questions and hypotheses to be addressed cannot be fully studied *in vitro* alone and require *in vivo* studies.

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

Several factors lead to a reduction of animal numbers, including reducing variation and good experimental design involving the use of appropriate statistics. In particular statistical tests

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will be used to ensure that we use the minimum number of animals possible to reliably interpret our data.

Refinement

Explain the choice of animals 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.

Refinement

There are several models AD and currently the most relevant models available to study AD are mice and rats. They are also the lowest vertebrate species that share common pathways to humans with respect to inflammation. We will use well-established methods to cause inflammation without causing severe or long lasting harm to the animals. Sometimes we will test the behaviour of the animals but the tests we will use do not cause any distress or lasting harm and usually rely on natural behaviour of the animals (exploration, social interaction) However, all animals will be constantly monitored to ensure that they suffer minimum distress