# G: NON-TECHNICAL SUMMARY (NTS)

Please attach the Non-technical Summary as generated by your application in ASPeL.

Word limit; 1000 words

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|---|---|
| Project Title | The role of inflammation in cerebrovascular disease |
| Key Words | stroke, vascular dementia, inflammation, cerebrovascular disease, neurovascular |
| 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.

**No** (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** (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):***

This project aims to find out how inflammation contributes to devastating conditions of the brain that are a result of disruptions in the supply of blood or function of blood vessels, so-called cerebrovascular disease. This includes stroke as well as vascular dementia.

We aim to find out how changes in inflammation in the brain and rest of the body are involved in the death of brain cells as well as the functional complications (cognitive decline, depression etc) seen in cerebrovascular disease. At present this is poorly understood and more research is needed.

***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)?***

Our research hopes to find new ways to treat stroke and vascular dementia, conditions that at present have no widely effective treatments.

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

Studies will be mainly in mice though some experiments will use rats. Over the five-year period of the project we expect to use 6900 animals in total. Approximately a third of these (2200 mice/200 rats) will be for breeding purposes and generation of transgenic animals with the rest (3900 mice/600 rats) being used in experimental procedures.

***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?***

In order to mimic human stroke and vascular dementia we will use experimental procedures to reduce the blood supply to the brain in rats or mice (cerebral ischaemia). This will mainly be done by opening up the neck of animals through a small incision to reveal the carotid artery. This artery is one of the main ways that blood gets from the heart to the brain. Then, using a number of different approaches, we will interrupt or perturb this blood supply. One way of doing this is through the injection of very small particles (or microemboli). These microemboli flow into the brain through the artery and then become stuck in blood vessels that are narrow. Alternatively, we can advance a fine filament (or suture) into the artery, which will reduce the amount of blood reaching a large area of brain. We can also physically reduce the diameter of the artery that will reduce the flow of blood to the brain. Another way to disrupt blood flow to the brain is through haemorrhage (i.e. the rupture of blood vessels),

and in rodents we can achieve this by directly injecting into the brain very small amounts of substances that cause minor blood vessels to burst. In addition to accessing the main arteries supplying the brain through the neck we can also do it through a small hole in the skull (a so-called craniotomy). For all the techniques described animals will be fully anaesthetised and will receive drugs (analgesics) to minimise any pain due to the surgery that is required. We expect most of the animals to fully recover from surgery and then they will usually undergo some tests of behaviour. These behavioural tests are designed to assess any problems with movement or sensation as would be seen in stroke patients, or memory problems as seen in vascular dementia, as well as other complications commonly reported by patients, including fatigue and depression. None of the behavioural tests are harmful to the animals and often just require observation for a short period in specialised apparatus. Tests can take place a few days or sometimes weeks after the initial surgery. In a few studies we will re-anaesthetise animals and use specialised imaging techniques to look at changes in how blood vessels function in the brain or the amount of brain cell loss etc. Animals may also receive simple injections or have blood samples taken. Clinically stroke, by its very nature, is a devastating disease, resulting in significant mortality and morbidity in patients. In trying to model stroke in animals a balance has to be struck therefore between establishing a valid model and in minimising pain, suffering, distress or lasting harm to the animal. However, as far as we are aware, effects of the stroke itself mainly result in discomfort to the animals, with severity kept to a minimum to ensure no lasting harm. The experimental approach to induce cerebral ischaemia is obviously specific to the experimental studies and it is inevitable that animals will suffer some level of pain due to the surgical procedures involved. At all times it will be our aim to reduce this to a minimum by the use of pain-relieving drugs. At the end of experiments animals will be killed by overdose of anaesthetic and we will take blood, brains and other organs/tissues to investigate various measures that will help us meet our overall aims.

## Application of the 3Rs

### *Replacement*

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

### *Replacement*

Studying mechanisms involved in brain diseases such as stroke and vascular dementia is extremely complex. Alongside the death of cells in the brains of stroke and dementia patients, these diseases are characterised by profound changes in behaviour, which it is not possible to study in cells in isolation. The proposed animal studies are complementary to a broad programme of work on stroke/dementia using human samples, isolated cell systems and non-protected model organisms such as zebrafish embryos.

### *Reduction*

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

### *Reduction*

Pathological and behavioural end points proposed in this project are well established in studies of stroke/vascular dementia and experiments are planned based on our own extensive experience or previously published data. We will use the minimum number of animals that can answer the desired scientific objectives and will extract all relevant information in the data by using appropriate statistical analysis. Studies will be designed using the newly released Experimental Design Assistant (EDA) from the NC3Rs (https://www.nc3rs.org.uk/experimental-design-assistant-eda). We will also consult regularly with qualified statisticians with regard to experimental design and statistical analysis.

### *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*

A critical feature of this work is that it is focussed on changes in function of blood vessels in the brain and the supply of blood that result in stroke and vascular dementia – so called neurovascular function. Animals with a lower degree of neurophysiological sensitivity (e.g. drosophila, C.elegans) do not allow one to mimic this. In contrast mice and rats allow one to model stroke/vascular dementia more closely, since neurovascular function in rodents is comparable to humans. All animals will be closely monitored for adverse effects and procedures put in place to minimise these, using very recent guidelines produced by the stroke research community. These guidelines draw on a wealth of experience in modelling stroke in rodents and have been produced through an NC3Rs working group that includes veterinary surgeons and other experts in animal welfare.