

G. NON TECHNICAL SUMMARY (NTS)

Project title: Neurological disorders: mechanisms and therapies

Duration of project - years: 5

Duration of project - months: 0

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

(a) basic research: **YES**

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

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

(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: **NO**

Keywords:

behaviour, cognition, brain, neurological disorder

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

Sufferers of neurological disorders frequently have disruptions in their genes. We are beginning to discover which genes these are, but we currently lack understanding of how these gene disruptions result in abnormal behaviours. The overall aim of the project is to understand how genetic disruptions linked to neurological disorders affect brain function and behaviour.

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 potential benefits of this project are two-fold. (i) Scientific knowledge of how genetic disruptions linked to neurological disorders affect brain function and behaviour will be advanced. This will inform scientists who are interested in the molecular mechanisms of neurological disorders, as well as those interested in the normal function of the brain. (ii) Humans can benefit in the longer term by the insights provided by this work. Current treatments for neurological disorders are at best only partially effective or may produce serious side-effects in some patients. By finding out more about the causes of neurological disorders in animal models, this project will aid the development of better treatments.

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

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at <https://www.gov.uk/government/publications/government-security-classifications>. Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location. All government information may be subject to an FOI request and subsequent assessment.

The project will use mice, some of which will have genetic alterations relevant to human neurological disorders. It is predicted that no more than 3000 mice will be used within the protocols of this project over 5 years.

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?:

No procedure is expected to exceed a 'Moderate' severity rating. Behavioural testing will be performed as a battery (i.e. each animal will be subjected to several different experiments); the total number of experiments and the number of experiments with aversive stimuli that any one animal will receive will be limited. The administration of certain drugs to modify behaviour will be carefully monitored for any unexpected reactions; the choice of drug will be informed by previously published studies and checked with the vet. The surgery to implant mini-osmotic pumps is well established and should not cause any lasting pain or distress. However, to improve post-operative outcomes, appropriate anaesthesia and analgesia will be used in consultation with the vet. Careful post-operative monitoring will be made to ensure no suffering. At the end of the procedures, animals will be killed by either a Schedule 1 or a non-Schedule 1 method or, if appropriate, the animals will be used for further breeding.

Application of the 3Rs

Replacement:

The project aims to understand how genetic abnormalities related to human neurological disorders alter brain structure and function. In particular, we will focus on behavioural outcomes. It is not possible to perform these experiments in humans; access to human brain tissue is very limited and there are strict limitations upon invasive approaches in clinical studies with human subjects. Behaviour can only be studied in living organisms, so experiments using neural cells derived from neurological patients would not be suitable because they do not exhibit behaviours. Computer models are not appropriate because there is insufficient information available on how the brain functions.

Reduction:

We will ensure reduction by writing a protocol for each experiment, which will include statistically designed group sizes (by power calculations) and by searching the literature to ensure that experiments are not unnecessarily duplicated. Breeding protocols will be designed to ensure that only the required number of animals is bred, to minimise wastage.

To avoid the necessity of breeding new cohorts for each behavioural test, each cohort will be subjected to a battery of tests, rather than a single test.

To avoid the necessity of maintaining animals solely for conventional breeding, animals that have been subject to non-invasive behavioural tests may be maintained for conventional breeding.

Refinement:

We will be using mice, which have a similar genetic makeup and neuroanatomy to humans. There are many behavioural tests that allow us to assess neurological disorder-related behaviours in rodents, something that cannot be done in lower model systems.

We are undertaking a series of experiments that have been shown by others not to cause suffering. Before all experiments, the rodents will be handled to reduce the stress of human interactions. Behavioural experiments in general do not cause pain and suffering, but suitable time intervals

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at <https://www.gov.uk/government/publications/government-security-classifications>. Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location. All government information may be subject to an FOI request and subsequent assessment.

12 December 2016

between experiments will be given, and there will be a limit on the use of aversive stimuli given to any one animal. For surgical procedures, suitable anaesthesia and analgesia will be administered in consultation with the vet; any sign of suffering will be discussed with the vet for immediate advice.

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at <https://www.gov.uk/government/publications/government-security-classifications>. Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location. All government information may be subject to an FOI request and subsequent assessment.