

G. NON TECHNICAL SUMMARY (NTS)

Project title: Neural Control of Sensorimotor and Autonomic Function in Health and Neurological Conditions

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: **YES**

(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:

neural injury, rehabilitation, neural plasticity, locomotion, bladder function

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

We aim to study the mechanisms and effects of different interventions capable of promoting repair of injured nerves in the brain and spinal cord to produce functional recovery. We will specifically investigate changes in stepping behavioural and other functions such as bladder control following injury and recovery through different interventions.

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 ultimate goal of our project is to provide interventions that can facilitate recovery of function following injuries to the brain and spinal cord. Some of the interventions included in this project, such as epidural electrical stimulation and rehabilitation have already shown promise in clinical application. However, further refinements are required to improve their effectiveness. Other newer potential interventions are in earlier development and require to be tested in animals.

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

Rats = 2500 Mice = 1800

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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.

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?:

Some animals will only reach a mild level in the severity scale. Others, will never wake up from the anaesthetic. For the nervous system injury procedures, most animals will be expected to be in the severe level of severity. This is mostly due to disruption of movement and sensation in some parts of the body. The level of disruption will also vary depending on severity of the injury. Control of bladder function is often compromised in these animals. Therefore, we care for each animal at least twice daily for the duration of the experiment to manual express their bladders and check for any abnormal behaviours. For example, persistent weight loss will be treated with supplemental diet, wet food and if necessary saline injections. However, we do not expect to induce pain in these animals. In severe lesions, the communication between the brain and spinal cord is completely severed and pain sensation cannot be processed by the brain. Because our primary aim is to facilitate recovery of function after lesions, the wellbeing and health of animals is of paramount importance. Ill health and pain are not conducive to such recovery. In the rare occasion when adverse effects exceed expected changes (for example, persistent excessive weight loss, inability to eat or drink, etc.) the animal will be humanely killed using an approved method. Therefore, we individually care for each animal at least twice daily for the duration of the experiments. At the end of all experiments, animals receive an overdose of anaesthetic for collection of tissues or are killed using an approved Schedule 1 procedure.

Application of the 3Rs

Replacement:

The complexity of the events leading to and as a consequence of lesions to the nervous system involves several physiological systems in the body. Unfortunately, reduced preparations such as cell in a dish, parts of brain kept in a dish, cannot provide enough information from all of the systems simultaneously. Our primary objective is to investigate functional recovery, which can only be measured in alive behaving animals.

Reduction:

Our experimental design has been optimized to use the lowest number of animals required to produce reliable statistical inferences. We combine several different techniques, including behavioural, physiological, anatomical tests and computational modelling. This allows us to reduce the number of animals required by eliminating the need to repeat experiments to collect different types of data. In addition, our experiments can provide very powerful results when looking at different types of measurements (behaviour, physiology, anatomy) from the same animal.

Refinement:

Rodents (rats and mice) are the preferred animal model for these projects for the following reasons. First, given the stage of our understanding a certain number of animals need to be studied, which precludes use of larger animals (pigs, cats, monkeys). Second, the nervous system of rodents have several similarities to humans, including the processes involved in responses to injury. Third, rodent models of nervous system lesions have been prevalent in the last years, and much is known about the disease process of the lesion in those species. All surgical procedures are done under anaesthesia and under aseptic conditions, which minimizes the need to deliver medication such as antibiotics. As mentioned before, each animal is individually taken care of at least twice daily. Also, pain and distress are unwanted outcomes because they are detrimental to functional recovery. Therefore even the smallest changes, for example in skin condition, such as a small sore, are immediately treated.