G. NON TECHNICAL SUMMARY (NTS)

Project title: Recovery of peripheral nerve function
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: 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: NO

Keywords:
Nerve, bladder, physiology

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

Loss of mobility and control of bladder or gut are all major concerns for patients with nerve injury. One
solution could be peripheral nerve interfaces, devices that are implanted into cut or surgically teased
nerves so that activity in the nerve fibres can be recorded or stimulated. In this project interfaces are
being developed for bladder control, for restoring movement in amputees and for controlling visceral
functions via the vagus nerve.

This project aims to develop interfaces suitable for human use, to prevent the scarring reaction that
currently limits their useful life, and to develop wireless communication from interfaces to receivers
outside the body.

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 aim ultimately is to restore function to human and canine patients that have lost bladder control
after spinal cord injury, or who have lost limb function through nerve injury or amputation, although only
rat and mouse models will be used in this early study. A nerve interface is used to pick up signals for
limb or bladder control, and this is used to drive stimulators or nerve block to prevent unwanted bladder
emptying, empty on command, drive robotic limbs, or control muscle contraction in a paralyzed limb. In
addition vagal nerve recording and stimulation is being developed for control of the immune system, gut and other organs.

What types and approximate numbers of animals do you expect to use and over what period of time?
800 adult rats 450 adult mice Over five 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?
The procedures are of moderate severity or, where possible, carried out exclusively under humane, terminal anaesthesia. The main adverse effects from nerve surgery are sensory changes that on very rare occasions lead to animals biting their toes. This can be minimized by choosing strains that do not do this and by humanely killing the animal if it is observed. Animals will be humanely killed at the end of the procedures, and most will be examined by histology.

Application of the 3Rs
Replacement:
The aim of the licence is to develop nerve interfaces for limb, bladder and visceral control. This can only be done by implanting prostheses into nerves in which there is electrical impulse activity, driving muscle contractions and bladder control. Tissue culture experiments would be meaningless because there would be no nerves to interface with, and no activity to record. In addition we need to develop methods to stop the scarring reaction that currently limits the useful life of prostheses. This only happens in animals with a working inflammatory system and a scarring reaction.

Reduction:
The main method for minimising numbers is careful preparatory work in pilot experiments with small numbers of animals, or terminal experiments on a few animals. By using fully developed methods, and behavioural experiments that we have fully validated in previous work we can get highly repeatable results, so the groups of experimental animals can be small.

Refinement:

Rats are the best experimental animal for nerve interface development, because the nerves are reasonably large, there is sufficient space in the body or under the skin for connectors and interfaces, and the patterns of nerve impulses in response to movement are similar to those in humans.

Mice are used when it is important to use genetically modified animals, particularly in experiments in which we are working out which mechanisms in the immune system are responsible for scarring in response to prostheses.

All experiments are done on one side of the animal only, which means that there is little disability and no loss of bladder control.

By choosing the correct strains of animals we can minimize the tendency of animals to bite their toes after nerve surgery.