Home Office

NON-TECHNICAL SUMMARY

Peripheral Nerve Regeneration

Project duration

3 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants
- (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 following aims mentioned in paragraph (b)

Key words

peripheral nerve injury, stem cells, biomaterials, surgery

Animal types	Life stages
Rats	adult

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

To improve peripheral nerve regeneration following traumatic injury using stem cells and biomaterials.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

Why is it important to undertake this work?

Peripheral nerves carry information from the brain and spinal cord to their target organs. They are essential for movement, sensation and other important functions such as temperature control. Peripheral nerves are commonly injured following trauma (e.g road traffic accidents, workplace incidents) or following surgical removal of a cancer (e.g. prostate cancer). The subsequent disability following peripheral nerve injury can be significant and wide ranging effects including (but not limited to) complete loss of a limb's function, sexual dysfunction, inability to control and move facial muscles and pain. Current treatment options are limited and even with optimal access to current treatments, outcomes remain extremely poor.

What outputs do you think you will see at the end of this project?

The primary output of this project is to produce a medical device that (i) replaces the need for a nerve graft (where a healthy nerve is sacrificed in order to reconstruct an injured nerve) and (ii) improves upon outcomes for patients receiving this treatment. Outputs will also include scientific publication of our findings which will inform further research in the field.

Who or what will benefit from these outputs, and how?

Within the short term, researchers looking at further understanding the nature of peripheral nerve injury will be greater informed by the publication of our findings. In the long term, if successful, patients with peripheral nerve injury will benefit from an alternative treatment options to nerve grafting (which otherwise involves sacrificing the function of a working nerve).

How will you look to maximise the outputs of this work?

All work, unsuccessful or successful will be submitted for publication. This will prevent duplication of work by other groups and guide further research direction. Our work is a collaboration between two groups with extensive experience in biomaterials and peripheral nerve, by combining expertise we increase the chance of success.

Species and numbers of animals expected to be used

- Rats: 300

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

Explain why you are using these types of animals and your choice of life stages.

We have chosen to conduct the experiments described on adult rats for the following reasons:

- We have considerable expertise evaluating a similar medical device in rats, and taking this treatment into human trials. This expertise allows us to better plan the experiments required, such that only a minimum number of animals are required.
- The rat sciatic nerve model is similar in size to a human digital nerve and it is therefore pragmatic for suturing biomaterial conduit interventions.
- The rat model of sciatic nerve injury is used by many other researchers internationally and the outcome measures are well documented; therefore by utilising a well established model, it is easier for our research to be appropriately scrutinised and compared to other findings. Additionally, there is less need for other groups to duplicate this research, thereby reducing the overall need for further animal research.
- Rats undergo nerve regeneration at a fast rate. Therefore we can assess the outcomes of the experiment in less time, hence minimising animal suffering.
- Immature rats have an even greater capacity for regeneration, such that this may limit the ability to accurately evaluate the benefit of the experimental treatment. In addition, the nerves that we would seek to reconstruct are much smaller and the repair would be less representative of a human repair, nor would the creation of an appropriate sized defect be possible.

Typically, what will be done to an animal used in your project?

Rats will undergo a surgical procedure whereby a nerve to one leg will be cut and then repaired through a variety of methods, including the experimental treatments we are investigating. The majority of rats will then not require a further surgical procedure. They will be monitored closely to support their

welfare to the time points already listed. During this time, behavioural studies will also be conducted. For the majority of animals, at set time points, they will be humanely culled and their tissues closely examined to obtain the experimental outcomes. For a subset of rats, they will undergo a further general anaesthetic to allow testing of the nerves function. These rats will be humanely culled prior to recovery from anaesthetic.

What are the expected impacts and/or adverse effects for the animals during your project?

Animals are expected to experience mild postoperative pain in the short term and this will be ameliorated with pain-killers. There is likely to be some reduction in function to the limb with the nerve injury. In our experience this does not seem to effect the rats mobility or cause any signs of distress.

In the long-term models (3-6 months), animals could undergo autotomy, where the rat chews the nails of the numb hindpaw. We will mitigate this by housing in groups with a calm environment and the use of strains not thought to exhibit autotomy and, therefore, expect autotomy to be less than 10%.

Expected severity categories and the proportion of animals in each category, per species.

What are the expected severities and the proportion of animals in each category (per animal type)?

All animals are expected to experience moderate severity outcomes due to them all undergoing a surgical procedure resulting in reduction in the function of one limb

What will happen to animals at the end of this project?

- Killed

Replacement

State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.

Why do you need to use animals to achieve the aim of your project?

We have created an artificial nerve graft that has been tested successfully in the laboratory but prior to testing in a human would need further evaluation in an animal to ensure safety and effectiveness of its use in a similar environment to those injuries seen in humans. Human injuries tend not to be standardised and it is very difficult to control for a multitude of variables as is possible in an animal model.

Which non-animal alternatives did you consider for use in this project?

We have tested materials in the laboratory cell culture models with nerve cells and stem cells to choose the material most likely to be successful prior to animal trials. Moving forward from here, animal studies

are an essential next stage to ensure safety before considering placing these devices in humans.

Why were they not suitable?

Laboratory testing of materials to assess nerve cell and stem cell growth has been considered suitable and carried out, however, this information is not sufficient to move toward human trials. Animal studies would be required prior to human studies to maximise human safety.

Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.

How have you estimated the numbers of animals you will use?

Within each experimental group we will use 8 rats. There are 4 experimental groups. Each timepoint will require 32 rats. We estimate utilising at least 8 time points.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

Only one material hydrogel is being taken forward via this project as other potential materials were tested using non-animal laboratory techniques thereby reducing the number of animals required. Full review of the published literature has been undertaken to ensure that there is not undue duplication of experimentation.

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?

- Close monitoring of animal welfare to reduce the risk of loss animal loss.
- Any adjustments to materials considered would be tested in the laboratory before testing in animals.

Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare

costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

From our experience gained over the past years using these animal models, it is apparent that the experimental procedures described in this application do not greatly affect the well being of the animals. The majority of described procedures are carried out whilst the animals are fully anaesthetised. The animals do not appear to have persistent adverse effects from the anaesthesia. From past experience, after the nerve injury, the animals do not show any behavioural signs of pain whether the nerve repair is carried out immediately or with delay. Nerve injury with/without repair can partially affect the gait, but has little effect on the mobility of the animals. The insertion of the nerve conduit at the site of repair does not affect the mobility of the animal, because the biomaterial is soft and flexible, and after harvest histology, showed no signs of adhesion or inflammation in past experiments.

In the long-term models (3-6 months), animals could undergo autotomy. This will be mitigated by using strains of animals that are not expected to show autotomy and using refined animal care strategies.

Why can’t you use animals that are less sentient?

The intervention requires suturing of nerve endings to a device. At a more immature life stage repair is more difficult and less likely to be representative of the repair used in humans. Additionally, at a non-adult stage, the ability to self-regenerate nerve is much greater, and therefore would not accurately evaluate the efficacy of the device being tested. Recovery of function secondary to the intervention is an important experimental outcome therefore utilising only terminally anaesthetised animals would not allow this to be observed.

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?

All animals will be monitored closely for any signs of pain or distress, especially in the immediate post-operative period. Analgesia will be provided where necessary and consultation with the NVO if there are other concerns.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?

We will follow best practice guidance published by the National Centre for Replacement, Refinement and Reduction.

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?

The investigators are subscribed to updates from the National Centre for the Replacement, Reduction and Refinement of Animals in Research and will implement any advances in a timely manner.