Home Office

NON-TECHNICAL SUMMARY

Support procedures for Neural Repair

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

No answer provided

Animal types	Life stages
Mice	adult, pregnant, juvenile, neonate, embryo
Rats	juvenile, adult, neonate, embryo, pregnant

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 breed normal and genetically altered animals to provide animals and tissues in a timely fashion for research into neural repair and protection, and perform initial testing of therapeutic compounds for compatibility.

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?

The licence supports the work of a group working to develop methods to repair and protect against damage to the nervous system. The licence provides normal and genetically altered animals and tissues to support this work. The licence also allows initial testing of new therapeutic compounds to find out if they are compatible with mammals.

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

This is a licence to support the research of the group by providing animals and tissues in a timely fashion to enable research aimed at developing new treatments for damage to the nervous system. It also allows for the initial testing of new treatment compounds to assess their compatibility.

Breeding according to the principles of demand-matched supply will minimize wastage and reduce the need to obtain lines from commercial suppliers thus reducing contingent transport stress.

New potentially therapeutic substances will be tested for compatibility with animals.

The outputs will be achieved through other licences held within the group. These will be through scientific publications relevant to the repair of the protection and repair of the nervous system.

Data will be published from the *in vivo* biocompatibility tests in the licence.

Tissue from animals kept in this licence is used for *in vitro* tests whose results will be published.

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

The main output of the licence will be the enabling of research within the group through the timely provision of animals and tissues for research and through initial compatibility testing of compounds.

Published data from biocompatibility testing and on any new tests developed will by used by academic and pharmaceutical company groups.

The overall aims of the group are to develop new treatments for spinal cord injury, Alzheimer's disease and glaucoma.

For spinal cord injury the aim is to develop new methods to promote regeneration of axons in order to restore function.

For Alzheimer's disease the aim is to develop treatments to reactivate plasticity in the adult CNS. This enables the brain to make new circuits to bypass the damaged neurons. This restores cognitive ability and delays the onset of dementia, but does not stop the slow progression of the neuronal damage caused by the disease.

In glaucoma the aim is develop treatments that protect retinal ganglion cells from the effects of the disease and to enable damaged axons to regenerate in the optic nerve.

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

The output of this licence will be published in papers from the group, enabling future collaborations and new models for investigation. Any new or improved methods of animal husbandry, production of transgenic animals and unsuccessful approaches will be published in papers from the group. The research group collaborates with several other research groups in various countries. Transgenic animals can be transferred from other groups or to other groups to enable research. Members of the group work closely with other groups worldwide and attend meetings with other groups working in the same area. Successful and unsuccessful methods are regularly discussed and presented.

Species and numbers of animals expected to be used

- Mice: 4740
- Rats: 1850

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.

The main purpose of the licence is to provide transgenic and normal animals for use in experimental procedures in the laboratory. These animals are either used to provide tissue for tissue culture experiments or are transferred to other licences held in the group for experimental work.

For tissue cultures late-stage embryos or newborn animals are needed to provide nerve tissue that can survive in tissue culture

For animal experiments in the group on repair and protection of the nervous system adult animals are used, matched to behavioural and anatomical models optimised for testing repair and protection treatments.

For testing compounds for compatibility adult animals are used, because the compounds will be tested for their ability to protect and/or repair the nervous system.

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

Procedures are included that enable preservation of transgenic embryos and establishing transgenic lines from preserved embryos. These procedures involve minor surgery for vasectomy and implantation of embryos.

Most of the animals kept on the licence are transgenic or normal animals that are bred so as to provide the number of animals that are needed to provide cells for tissue culture, or to provide transgenic animals that will be transferred to other licences for experiments to discover new treatments for the repair and protection of the nervous system.

Some animals are used in pilot studies to test the compatibility of new potentially therapeutic compounds

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

Procedures for preservation and restoration of transgenic lines. In these protocols animals receive minor surgery for vasectomy and embryo implantation. In rare cases there may be wound infection or the wound may need to be resutured once.

Maintenance and breeding of transgenic animals. The majority of transgenic animals kept under this licence have no deficits and behave like normal animals. Two lines that are models of Alzheimer's disease and Motor Neuron Disease are kept. These animals do not show any deficit until they are over 4 months old, during which time breeding is accomplished. In rare cases pregnant animals may be kept while showing adverse signs until they have delivered their litter, but in they are always killed before they become severely disabled.

Testing of compounds for compatibility. All compounds to be tested have been shown to be non-toxic and efficacious in tissue culture experiments, and past experience tells us that these compounds will be well tolerated by test animals with no adverse effects.

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)?

The animals used for generation of transgenic lines receive an anaesthetic and therefore come into the moderate category; they are expected to make a rapid recovery.

Over 90% of the transgenic animals show no deficit and are therefore in the mild category.

Animal models of Alzheimer's disease and Motor Neuron Disease can show early signs of poor mobility and weight loss. They are almost always used at a time at which the deficit is very small. Occasionally pregnant animals may be allowed to survive to a greater degree of disability within the moderate severity in order to deliver their litter.

Protocol 1. Mild all animals

Protocol 2. Moderate all animals

Protocol 3. Moderate all animals

Protocol 4. Moderate approx. 30%, the rest Mild

Protocol 5. Non-recovery

Protocol 6. Mild all animals

Protocol 7. Mild all animals

Protocol 8. Mild all animals

Protocol 9. Mild all animals

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

- Kept alive
- Used in other projects

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?

In order to discover new treatments to preserve and repair the nervous system, mechanisms and treatments are tested in tissue culture. Appropriate animal tissue is needed for this work. When promising treatments are identified they need to be tested in animals to show whether they can repair or protect a real nervous system with all its complexities. Tissue culture models are not yet adequate to determine whether treatments may work.

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

Most of the work in the group is performed in tissue culture. Only final verification is done in animal models.

Why were they not suitable?

The mammalian nervous system is extraordinarily complex, and subject to effects from the immune system and other body mechanisms. Only by testing treatments in whole animals can treatments that might be taken forward for use in human and veterinary patients be identified.

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?

The purpose of the licence is efficient and timely supply of animals for tissue culture and work on other licences. The required number for animals for planned experiments are calculated on those licences. Numbers of transgenic lines must be sufficient to maintain a breeding population.

Numbers of animals used for establishing and preserving transgenic lines are calculated based on the likelihood of new lines being introduced, and the need to transfer or preserve lines if the lines are sent to other animal facilities.

Numbers of animals for provision of tissues is based on the current level of use of animals within the group.

Numbers of animals for testing of compatibility is based on initial testing of five new compounds during the time of the licence.

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

Breeding is carefully monitored so that sufficient but not excessive numbers of animals are bred for the planned experiments.

For pilot compatibility studies only 4 animals per group are planned, and animals will be dosed one at a time, so that if the first animal shows a reaction the experiment can be stopped or replanned.

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

In this licence efficient and timely breeding is performed. The reduction methods for the experimental work are described in the relevant licences.

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.

Most of the animals used in this licence have no adverse phenotypes. Two transgenic lines are used to model Alzheimer's disease and Motor Neuron Disease.

In the Alzheimer animals, the genetic alteration is chosen so that animals show a deficit in memory two or more months before they become disabled. Experiments can therefore be performed on animals that appear normal.

In the Motor Neuron Disease model, animals are killed to provide cells for tissue culture before any motor deficit occurs.

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

Fish, insects do not give very good models of neurodegenerative disease or recovery of function compared to mammals. The tissue culture methods for which this licence provides tissue only work well with mammalian cells.

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

The procedures have already been highly refined based on work over many years, and very few animals show signs of harm. Tests are being further refined to allow testing of treatments at early ages, before any harmful deficit is apparent.

For compatibility testing of compounds, all compounds are screened for toxicity and efficacy in tissue culture studies. Testing begins with a low dose in a single animal and only escalates if no toxicity is seen.

When GA animals are transferred from elsewhere, where practicable germ plasm will be imported instead of live animals.

Where urine is to be collected, consideration will be given to using Lab Sand rather than collection of urine in a gridded cage.

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

Animal testing is constantly being upgraded in the host laboratory and elsewhere. New methods will be incorporated into our practice.

Excellent information is available on the various websites listed above which are constantly updated with new 3Rs information.

Full and updated information for licence-holders is provided under the project-holders website.

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

The establishment offers continuous training and advice through the training facility and the animal facilities.

Excellent information is available on https://www.nc3rs.org.uk which is constantly updated with new 3Rs information. http://en.3rcenter.dk, http://www.frame.org.uk, http://3rs.ccac.ca, http://www.ahwla.org.uk.

Excellent information on procedures is available on https://animalcare.ubc.ca

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