Home Office

NON-TECHNICAL SUMMARY

Generation, breeding and maintenance of genetically altered mice

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Physiology, Breeding, Mice

Animal types	Life stages
Mice	Embryo and egg, Neonate, Juvenile, Adult, Pregnant 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?

The project is to breed and supply novel and established lines of genetically altered (GA) mice within the establishment and to collaborators.

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?

Genetically altered mice play a vital role in understanding the pathophysiology of many disease conditions, including cancer, cardiac and metabolic disorders, as well as advancing our knowledge of basic physiology. Under this licence, we will breed, and maintain genetically modified animals to the highest standards of health and welfare, ensuring reproducible and publishable research outcomes. Environmental enrichment will be provided as standard to promote animal wellbeing.

The establishment has access to in house specialist in cryopreservation of genetically altered lines, supporting long-term sustainability and reducing unnecessary breeding. Centralising breeding programmes within the establishment ensures that highly experienced staff manage all aspects of creation, breeding, and husbandry. This approach prioritises animal care and welfare while maintaining scientific integrity and efficiency. It also minimises wastage by enabling multiple research programmes to access the same animal lines, bred to specific project requirements within defined timeframes.

Our motivation is to support leading scientists in pursuing novel research that aims to benefit human and animal health.

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

Provision of GA models to researchers, resulting in new knowledge of physiological and disease mechanisms and dissemination via peer reviewed publications

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

Researchers at the establishment and their collaborators, other research facilities who do not have the resources to breed GA mouse lines.

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

Peer reviewed publication of the subsequent work on these animals, including encouraging publication of any failures of the approach, collaborations with other institutions.

Species and numbers of animals expected to be used

- Mice: 53700

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.

Mice are a well recognised species for work involving genetic alterations and there are standard protocols, methods and reagents used that have been optimised for this species and acknowledged benefits for use.

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

The majority of the animals will be used for the breeding and maintenance of genetically altered animals. A small number of mice may be administered with a transgene-inducing or deleting agent in their diet. Some mice have a gene which is inactive until the mouse is given one of these activating drugs. A small sample of ear tissue may be taken to confirm genotype of the mouse.

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

Breeding of genetically altered mice with no more than a mild phenotype. These animals are not expected to show any deviation from normal wild type mice. A typical breeding female will have 6-8 litters in her lifetime.

Administration of a transgene inducing or deleting agent may cause weight loss as a result of the administration and action of inducing or deleting a gene. Some mice have a gene which is inactive until the mouse is given one of these activating drugs.

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 majority, approximately 90%, of the mice are perfectly normal and will suffer severity which is sub-threshold. Mice receiving a transgene-inducing diet may have weight loss as a result of the administration of the diet.

A small proportion of the mice will be bred with an altered immune system, meaning they could be prone to infection. We will use barriered housing and sterile food and water plus aseptic handling to reduce this risk.

What will happen to animals used in this project?

- Killed
- 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?

Work on this project will breed and supply novel and established lines of genetically altered (GA) mice within the establishment and to collaborators. Research carried out in this establishment covers a wide range of fields and seeks to answer questions regarding normal physiological processes, as well as those underpinning the development of various diseases. The majority of these questions, particularly as GA techniques such as inducible gene switch systems have developed, are now related to specific genes and/or their targets and how they can modulate normal processes or influence susceptibility to a disease. Although non-animal alternatives can be used to interrogate these processes, particularly at a more reductive level, they are unable to adequately model the complete array of interactions necessary to fully understand how genetic modifications result in normal or pathophysiological processes.

New technologies are improving the field of animal transgenesis and they will allow the generation of new mouse models to be applied in biomedical research. First steps in a scientific project will involve in vitro approaches, the final characterisations and applications will require the use of GA animals. The different animal models will integrate the complete range of molecular, cellular, physiological and behavioural interactions necessary to fully understand how genetic modifications result in normal or abnormal processes

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

Prior to the creation or importation of a GA line, researchers will be required to ensure their research questions cannot be addressed using non-animal alternatives. This assurance will include extensive literature searches, including the use of relevant methodological terms across a variety of sources including field specific journals and websites which collate replacement methods (Replacing Animal Research checklist & systematic review, NC3Rs gateway). They will also be required to meet with the Establishment 3Rs manager to discuss any potential replacement models. Results of any searches will be reviewed, but it is expected they will include a thorough review of the following potential alternatives:

- In vitro assays
- Invertebrate models including drosophila (fruit flies) or other less sentient species.
- Replacement models including pre-protected (not protected by legislation as they are not yet considered to be capable of feeling pain or distress) species e.g. zebrafish embryos
- In silico (computer) models
- Human cells or tissues

Prior to importing a new strain, consideration will be given to the scientific evidence gathered from in vitro data e.g. receptor binding assays to identify appropriate targets and PCR analysis of gene expression. The breeding method and proportion of affected animals produced will also be considered.

All of these factors will be used to justify the introduction of strains under this licence with advice and discussions taken with the researcher and NVS (Named Veterinary Surgeon) as required.

Why were they not suitable?

In-vitro assays cannot adequately model the complete array of molecular, cellular, physiological and behavioural interactions necessary to fully understand how genetic modifications result in normal or abnormal processes.

Invertebrates are a useful adjunct to animal studies in that large throughput of gene alterations can be screened but the differences in circulatory, neurological systems etc limit their use.

The establishment has a very active replacement model section encompassing disease models using Drosophila (fruit flies)and other less sentient species, but in some cases the targets need to be validated in a mammalian system.

All non animal alternatives will have been investigated before embarking on work requiring the services of this PPL.

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?

These numbers are predicted, based on analysis of the number of animals used in the last five years to meet the demand of our researchers.

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

Using efficient breeding techniques following the guidelines set out by the Home Office and NC3Rs. We also have specially trained and experienced colony managers.

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

New software for colony management is making tissue sharing more efficient. We follow a surplus mouse sharing protocol that ensures we optimise animals used

Single establishment-wide maintained colonies for multiple users rather than individual colonies for each group.

Upskilling of staff to specialise in colony management which includes training from world leading establishments and organisations providing knowledge and awareness of the latest guidelines. Appropriate colony management training decreases over-production, improves breeding selection and efficiency, helps identify issues early, and is key for adopting current best practice.

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.

This service licence will be used to breed and supply genetically altered mice for research.

Mice are a well-recognised species for work involving genetic alterations and there are standard protocols, methods and reagents used that have been optimised for this species and there acknowledged benefits for use.

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

The resulting offspring will be used in research projects for which the whole mammalian body systems are required.

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

One of the chief benefits of undertaking this work under a service licence is that all the techniques to be used are undertaken by a small group of highly experienced technical staff which minimises suffering.

We maintain animals is socially and behaviourally appropriate housing conditions and use enrichment as standard in line with the establishments environmental enrichment guidelines.

We are now able to use a non-invasive method of genotyping for certain lines.

Additionally, provision of genetically altered animals, and their tissues, is frequently a more appropriate replacement of mice in more invasive regulated procedures. In this scenario, genetically altered mice

without welfare impacts are humanely killed and their tissues investigated.

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

I will consult with colleagues across the field and sources such as

AWERB

International society for Transgenic Technologies

Animal Welfare and Management Discussion Group

NC3R's Efficient Breeding Strategy

Institute of Animal Technology

Efficient Breeding of Genetically Altered Animals Assessment Framework(Home Office)

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

Advice has been sought from Establishment 3Rs manager on the development of this PPL application. The NC3Rs are constantly checked for any advances in the 3Rs, particularly in refinement of transgenic animal breeding and non-animal methodologies.