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NON-TECHNICAL SUMMARY

Breeding and Maintenance of Genetically Altered Animals for Regenerative Neuroimmunology Research

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Mouse breeding, Genetically altered mice, Colony maintenance

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 breeding, generation, and maintenance of mice with genetic modifications. These mice will supply project licenses within our group with the appropriate mice needed to carry out the experimental work.

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?

This work is important because it establishes a reliable foundation for research into neurological diseases. Creating a steady supply of genetically modified mice (mice whose genes have been specially altered for research) ensures that studies proceed smoothly and on schedule. Collecting tissue to grow cells in the lab allows early testing of how substances affect cells, helping to identify toxic effects before live animal testing, which improves safety and reduces the number of animals used. Studying cellular responses to inflammation in vitro (experiments done outside an organism) helps identify key processes and potential treatment targets early in the research. Additionally, this work will improve disease models and enhance understanding of normal development and how a disease works in the body (disease mechanisms) in both young and adult mice. Confirming experimental targets will guide future studies and increase the relevance of findings to human health. Ultimately, the goal is to better understand how chronic inflammation affects the body, especially in conditions like multiple sclerosis (MS), and to contribute to the development of more effective treatments. This research has significant potential to advance medical science and improve patient outcomes.

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

The primary output of this breeding license will be the reliable supply of genetically modified mice and collected tissues that support other experimental studies within our research program. These animals and tissues will be essential resources for a range of experiments aimed at understanding neurological diseases. By maintaining groups of lab mice whose health and genetics are well known and carefully checked, we ensure that subsequent research projects have consistent, high-quality biological material, which is crucial for producing robust and reproducible results. This foundational work enables the broader scientific goals of the group and contributes to the success of multiple experimental licenses. In addition to providing mice and tissues, the other experimental licenses supported by this breeding license are expected to generate important new information about how neurological diseases, such as Multiple Sclerosis, develop and progress.

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

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This work will benefit people with neurological diseases, especially those with conditions like multiple sclerosis (MS), both in the short and long term. In the short term, creating a steady supply of specially bred mice and improving lab testing helps research progress smoothly and quickly, allowing new treatments to be developed faster. Testing substances on cells grown in the lab first helps identify any harmful effects early, reducing the number of animals used and improving safety. In the long term, this research will improve disease models and deepen our understanding of how chronic inflammation affects the body. This knowledge will guide future studies and help develop more effective treatments, ultimately improving health and quality of life for patients. Other researchers will also benefit from better tools and clearer targets, making their work more reliable and relevant to human health, advancing medical science as a whole.

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

We will keep detailed records to track the use and availability of these animals and tissues, allowing us to plan breeding schedules to meet demand without excess. Additionally, we will share information about breeding success, challenges, and best practices through internal meetings and relevant publications, helping improve breeding strategies both within our group and for the wider research community. Mouse passports will be used to communicate relevant strain-specific information to recipient research groups, to ensure appropriate care and use of the animals, thus maximising the scientific outputs derived from the work. This collaborative and transparent approach will maximise the value gained from the animals bred under this licence. Some genetically altered strains produced internally (and not sourced from commercial suppliers) may be made available to the wider scientific community through cryopreservation.

Species and numbers of animals expected to be used

- Mice: 10125

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 use mice because their bodies work a lot like ours, especially when it comes to how organs, genes, and the brain function. This makes them extremely useful for studying complex biological processes that we can’t fully copy in a dish or on a computer. Mice share significant physiological, genetic, and anatomical similarities with humans, especially regarding organ systems and fundamental biological pathways such as immune response. This allows for accurate modelling of human diseases, such as Multiple Sclerosis (MS), and the investigation of treatments within a whole, living organism. Unlike fish or invertebrates, mice have the physiological and immune system complexity needed to accurately model mammalian biology. This is especially important for studying how the body handles medicines, how the immune system works, and how the brain and immune system interact. Mice are also practical to work with in larger numbers, and there are many specially designed strains that allow scientists to

precisely modify or delete specific genes to study their roles in health and diseases such as MS. Different life stages—pregnant adults, newborns (neonates), and juveniles—are all needed in breeding mice because each stage plays a specific role. Pregnant adults are required to produce the next generation of mice. Newborns are important for early-life studies and for making sure the colony continues to grow. Juveniles are needed to maintain the colony and eventually become adults that can breed.

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

We use standard breeding and care practices to keep mouse colonies healthy, ensure consistent growth, and maintain the right number of mice at each life stage. Mice in this project will undergo the following:

Egg Collection (Superovulation): To collect eggs or early-stage embryos, female mice will receive two hormone injections into the abdominal cavity or under the skin about two days apart. If embryos are needed, these females will then be mated. The mice will be humanely killed using approved Schedule 1 methods at the right time to collect the eggs or embryos. Schedule 1 methods are legally approved and carefully controlled to ensure the process is quick, safe, and ethical

Embryo Transfer: To prepare female mice to receive embryos, they will be mated with sterile males, which makes their bodies ready for pregnancy without actual fertilization. Embryos will then be transferred into these females, either using a non-surgical method with or without mild anaesthesia, or a surgical method under full anaesthesia. Pain killers will be used for surgical procedures. If embryos are not needed, the female will be allowed to give birth and raise the pups. If embryos are required for research, the female will be humanely killed by a Schedule 1 method at the appropriate time.

Vasectomy (Sterilization of Male Mice): Male mice will undergo surgery to make them sterile. After at least two weeks of recovery, their sterility will be confirmed by mating with females. These sterile males will then be used to mate with females in order to prepare them for embryo transfer. The males will be used for this purpose until they are no longer suitable due to age or size, at which point they will be humanely killed.

Breeding and Use of Genetically Altered Mice: Genetically modified mice are produced either by naturally breeding males and females with specific genes or by altering embryos in the lab and placing them into a female mouse to develop and be born. The genetically altered mice produced under this research are not expected to show any signs of illness or harm due to their modifications. To determine the genetic status of a mouse, a small sample is taken using one of several methods, such as a tiny piece of ear tissue, a blood sample, a few hairs, or a mouth swab. In rare cases, if there is a technical problem during analysis, a second sample may be collected, always using the least invasive method possible to minimize any discomfort to the animal. Some animals may have an altered immune system making them more susceptible to infection. Animals with altered immune status will be housed in a barrier environment thereby minimising the likelihood of compromising health. These mice will be cared for appropriately and may be kept for up to 15 months. Mice may be humanely killed using a Schedule 1 method, used in other projects, or kept alive at licensed establishment for reuse

Very young mice, up to 5 days old, may be mice are humanely killed by decapitation and used to grow cells in the lab. Older mice and pups may be used to collect tissues for further analysis. All cells and

tissues will be collected during a terminal procedure, while the animal is fully under deep anaesthesia, so it feels no pain. A terminal procedure means the animal will be humanely euthanized as part of the process. No signs of illness or distress are expected during the procedure.

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

The majority of animals used in this project are expected to experience no more than mild and short-term effects such as brief stress from handling, minor discomfort from routine health checks, or temporary changes in activity or eating habits. These effects are usually very short-lived—lasting minutes to a few hours at most—and do not cause lasting harm. Some animals may undergo surgical procedures that may result in short-term moderate pain, suffering or distress. Mice that undergo surgery to receive embryos or a vasectomy may have some brief pain and discomfort afterward; however, this will be effectively managed using appropriate anaesthesia and peri-operative analgesia in line with veterinary advice. With this pain management in place, any post-operative discomfort is expected to be transient and resolve within a few days. Animals will be closely monitored during recovery to ensure appropriate healing and wellbeing. Some animals may have changes to their immune systems, which could make them more likely to get infections. To protect these animals, they will be kept in a barrier environment designed to reduce the risk of illness and keep them healthy.

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)?

Severity: Mild, 99%. Severity: Moderate, 1%.

What will happen to animals used in this project?

- Killed
- Used in other projects
- Kept alive at a licensed establishment for non-regulated purposes or possible reuse

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 use animals, specifically mice, because they allow us to study how complex biological processes work in a living organism—something that cannot yet be fully replicated in a dish using cells alone. In particular, we rely on mouse models to understand how certain genes, cells, or treatments behave in the context of a whole body, including how they affect the immune system, development, or disease progression over time. These insights are essential for identifying which biological targets are most relevant to human disease. Once we have this information, we can then move to non-animal methods,

such as using human stem cells in the lab, to carry out more detailed studies—helping us reduce the number of animals used overall.

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

We have developed and are continuing to refine lab-based (in vitro) models of human diseases using human stem cells. These models allow us to study disease processes directly in human cells grown in a dish, providing a powerful non-animal alternative. Wherever possible, we use these in vitro systems to investigate the biological mechanisms involved in disease.

Why were they not suitable?

Non-animal methods, such as using human cells in a dish, are incredibly useful and we use them wherever possible. However, these systems can't fully replicate the complexity of a living body. They don't show how different cells, tissues, and organs interact, or how the immune system responds over time. To fully understand how diseases develop and how potential treatments might work in the body, we need to study these processes in an intact, living system.

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?

We have estimated the number of animals needed based on our previous experience with similar studies, as well as data from published research. By looking at the results from earlier work, we can judge how many animals are typically needed to see clear and reliable differences between groups. We also use specialist software to help guide our planning, taking into account the likely success rates in breeding and the expected outcomes of each experiment. Throughout the project, we will regularly review our animal use to ensure we are using the smallest number necessary to achieve meaningful results, while still ensuring the research remains scientifically valid.

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

Before starting any animal work, we clearly defined our research goals, hypotheses, and the specific outcomes we needed to measure. This careful planning ensured that every animal used would provide meaningful data—information that is reliable, relevant, and directly answers our research questions—helping us avoid unnecessary or repetitive experiments. We also reviewed our own past data and relevant published studies to estimate the number of animals required and understand potential variability. By focusing on meaningful data from the start, we could design experiments that are

efficient and informative, allowing us to plan for the smallest number of animals needed to obtain robust and trustworthy results.

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

In addition to careful experimental design, we will minimize the number of animals used by employing efficient breeding strategies to produce only the mice we need, avoiding unnecessary surplus. These strategies include carefully selecting which males and females to mate, timing matings so that births occur predictably, and keeping detailed records of each mouse's family history to prevent unnecessary breeding. Other approaches include using surrogate mothers to carry embryos, pairing mice at their optimal reproductive age, and using non-surgical embryo transfer to reduce stress.

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.

We will primarily use genetically modified mice to study specific genes and biological processes related to human diseases. Our methods include breeding these mice, collecting tissues and cells for lab studies, and performing embryo transfers using both non-surgical and surgical techniques. All procedures will follow strict welfare guidelines, including careful monitoring and humane endpoints. The mice and methods chosen are designed to minimize any pain or distress. Pain killers are used to prevent pain. All surgical procedures are done under anaesthesia to prevent pain. Animals are given time to acclimate to their environment and handling to reduce stress. We monitor their health closely and stop any procedure early if animals show signs of distress. These approaches have been carefully refined and tested to ensure high standards of animal welfare while still allowing us to conduct meaningful research.

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

Unlike fish or invertebrates, mice possess the required physiological and immunological complexity to accurately model mammalian systems, which is critical for studies involving drug pharmacokinetics, the immune system, and complex CNS-immune interactions. Scalability and the availability of sophisticated genetically engineered mouse models are a principal reasons for the use of mice. These allow for the precise deletion or modification of specific genes to study their function and role in health and disease.

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

To minimize any harm or discomfort to the animals, we will use a variety of refinement measures. This includes setting clear limits to stop any unnecessary suffering early. We'll use the smallest and safest needles to reduce pain and the risk of infection. The animals' cages will be enriched with items that encourage natural behaviours and help keep them mentally healthy. When handling the animals, we'll use gentle techniques like tunnel handling and cupping, which are proven to lower stress. Animals will have at least 7 days to get used to their new surroundings and to the handling methods before any procedures begin. For animals brought in from outside, we'll allow extra time for them to settle in. We'll also gradually acclimate the animals to any restraint or treatment procedures to make sure they are as comfortable as possible.

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

We will follow established best practice guidelines to ensure our experiments are as refined and humane as possible. This includes guidance from organizations like the NC3Rs (National Centre for the Replacement, Refinement and Reduction of Animals in Research), which provides detailed advice on animal welfare and experimental design. In particular, we will implement NC3Rs best practice guidance on breeding and colony management to optimise the use of animals, improve genetic management, accurately forecast colony size requirements, and minimise the production of surplus animals. Careful colony planning, appropriate use of genotyping strategies, and regular review of breeding performance will help reduce unnecessary animal use and avoid wastage.

We will also adhere to the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines to improve the planning and reporting of animal studies. Additionally, we will consult relevant regulatory frameworks and institutional animal care policies to make sure our procedures meet or exceed current standards for refinement. By following these widely accepted best practices, we aim to minimize any harm to animals while maximizing the quality and reliability of our research.

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

To stay informed about the latest advances in the 3Rs (Replacement, Reduction, and Refinement), we will regularly review scientific literature and attend relevant conferences and workshops. We also follow updates from key organizations like the NC3Rs and other research networks focused on animal welfare and alternative methods. Throughout the project, we will actively share this information within our team and adjust our research practices accordingly to incorporate new 3Rs techniques and technologies. This ensures that we continually improve our approach to minimize animal use and enhance animal welfare. The establishment's Named Information Officers also help by sharing 3Rs updates and guidance with our team.

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