Home Office

NON-TECHNICAL SUMMARY

Breeding, maintenance and phenotyping of genetically altered mouse models for dementia drug discovery

Project duration

5 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

Key words

Dementia, Neurodegeneration, Alzheimer's disease, Parkinson's disease, Transgenic 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 purpose of this project is the generation, breeding and maintenance of genetically altered mice to support the identification and development of drug treatments for neurodegenerative diseases. This includes, but is not limited to diseases of the brain which mostly occur in old age, including Alzheimer's disease, Parkinson's disease and related conditions.

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?

Neurodegenerative disorders are a group of brain diseases which include Alzheimer's disease, Parkinson's disease, Motor Neuron disease, Huntington's disease and a number of similar conditions. They are a significant global health problem. There are already approximately 50 million people worldwide with Alzheimer's disease, the most common of these conditions, and as the general population ages, this has been predicted to increase to 150 million by 2050.

These conditions cause a great deal of suffering to patients and their loved ones and a high burden to society through the cost of care.

There are very few treatment options available for people living with these conditions. Despite some recent advances, there are currently no widely-available treatments that stop or reverse the progression of neurodegeneration and most of the medications currently available only treat the symptoms rather than curing the disease.

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

This licence will be used to produce genetically altered mice, whose genes have been changed to allow us to understand gene function in diseases seen in humans, along with genetically normal control mice for use on this licence and other licences which are required for drug discovery projects in neurodegeneration research.

Under this licence we will also carry out phenotyping studies on these animals. Phenotyping studies look at characteristics commonly seen with disease progression such as memory loss, movement coordination, behaviour changes, which can be measured as an indication of disease progression in these mice. These studies may be used to provide the following information:

- Whether these mice are suitable to use in further studies.

- How we use the animals, e.g. what age to use them at, what behavioural tests to use.
- In the case of mice in which we have genetically altered a potential target for new therapies, whether this is a suitable target for further work.

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

Short term (1-2 years): This will benefit our institute by providing a supply of animals for use in our drug discovery projects. These mice may also be shared with other researchers in the same field. Phenotyping data will also help us to evaluate whether it is appropriate to commit funding and resources to working on a new drug target.

Medium term (3-10 years): The supply of animals will enable us to pursue several projects (normally 3 to 5 are run simultaneously) to identify new therapies for neurodegenerative diseases. It is hoped that this will generate new drugs that can be tested in the clinic through partnership with pharmaceutical companies. Data generated from our work will also be published to benefit the scientific knowledge in the neurodegeneration field.

Long term (more than 10 years): It is our hope that our discoveries will lead to new therapies for neurodegenerative diseases that will benefit patients, their caregivers and society as a whole.

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

Our institute is an academic group with expertise in preclinical drug discovery methodologies used within the pharmaceutical industry and applying these in an academic setting. We work with a wide network of collaborators in the academic sector to investigate and validate interesting and novel drug targets and have strong connections within the pharmaceutical industry to facilitate the eventual development of these ideas into drugs to benefit patients suffering from neurodegenerative disease.

As an academic group we seek to publish our findings whenever possible.

Chemical structures of molecules originating in our laboratory and the properties of these molecules may be published in the form of patents. This is necessary to protect intellectual property but also provides a valuable source of information on the viability of drug targets and chemical structures and activity to the wider pharmaceutical industry.

Where projects are unsuccessful or no longer of interest to us, we will seek every opportunity to disseminate the work at scientific and public meetings as well as publish data in scientific journals.

Species and numbers of animals expected to be used

- Mice: 8450

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.

All of the procedures on this project will be carried out using adult mice.

We use wildtype (genetically normal) mice for many of our studies, but some of the mice that we use are genetically modified.

Many of the genetically modified mice generated under this project licence will not suffer any adverse effects as a result of their genetic modification. However, we may need to keep some of these animals until the point at which they begin to develop some of the features of neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease and display disease symptoms such as difficulty walking.

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

Mice used for breeding to maintain the colony: these will be humanely killed after they have been used.

Mice generated for use on other project licences: these will be bred and kept on this licence before being transferred to another licence. In most cases, this will be before any symptoms develop.

Mice used to provide tissues, body fluids or live cells: these will be humanely killed at the age at which we need to collect samples.

- Some of these mice will already have started to show disease symptoms before they are humanely killed.
- Mice used to provide cells will be humanely killed as embryos before birth (along with the pregnant mother), or a few days after being born.

Mice used to generate new genetically modified strains may undergo surgery to make them infertile (males) or to implant embryos (females). These are short procedures carried out under general anaesthetic and the mice quickly recover.

Mice used for phenotyping studies: these mice may be studied intermittently over a period of several months and one or more of the following procedures may be carried out:

- Some of these mice will be kept beyond the point at which they show disease symptoms.
- In some cases, the genetic alteration can be "switched on" by giving a drug such as tamoxifen, either by injection or in the food. This ensures that any harm resulting from the genetic modification is experienced only during the experiment, rather than for the lifetime of the animal.
- Behavioural Tests. We may carry out one or more behavioural tests which may be repeated over the lifetime of the animals. These generally do not cause any harm or distress to the animals. As part of this we may need to restrict the animal’s food intake. Food restriction may be necessary

when giving food is a reward or the incentive to drive the animal to learn the behavioural test. For the animal to be motivated it must have a need to desire the food prior to the test.

- Anaesthesia for imaging. Some animals may undergo live imaging tests, for which they need to be anaesthetised for around 1 hour. This may be repeated during the lifetime of the animal.
- At the end of the phenotyping study, the mice will be humanely killed, including by injecting a substance into the circulation through the heart (under anaesthetic) to preserve the tissues.

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

Genetically altered mouse models of neurodegenerative disease show a progressive worsening of symptoms with age. When using these mice, we will use models with the mildest symptoms and at the earliest ages that are compatible with our scientific objectives.

Different strains of mice begin to experience disease symptoms at different ages. Weight loss is often the first indication of poor health. This may be accompanied by various movement difficulties - such as a wobbly gait and tremor. There may be more general signs of poor health such as a hunched posture and poor condition to the coat.

In some of our phenotyping studies we may dose a substance to switch on the genetic alterations carried by the mice. One of these substances, tamoxifen may cause weight loss for a few weeks after dosing.

In some behavioural tests we restrict the amount of food given to mice and use a food reward to motivate them to carry out a task. This may also cause weight loss.

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 expected severities are mild (90% of mice) and moderate (10% of mice)

What will happen to animals used in this project?

- Used in other projects
- Killed
- 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?

When investigating novel drug treatments for disease it is necessary to understand how manipulation of the target for the drug impacts on the biology of the whole animal. There may be unwanted effects of drug treatment in other tissues or organs which would indicate a risk of side effects if the drug were to be dosed in humans. Furthermore, we need to gain a thorough understanding of what happens to the drug when it enters the body, including the rate it is absorbed from the gut into the bloodstream, where it is distributed in the body and how quickly it is eliminated.

When considering the effects of drugs or manipulating drug targets in the brain it is important to recognise the unique complexity of this organ, with many different cell types and networks of connections between nerve cells which cannot be fully replicated outside a living animal. Furthermore, if we want to understand how potential drugs may impact on symptoms of dementia we need to be able to test their effects on learning and memory in mouse models of disease.

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

We already employ experiments using cells and postmortem rodent and human tissue alternatives for much of the work at our institute. The following assay systems and models have been employed:

- Biochemical, cell free assays for investigating possible drugs created at our institute.
- Commercially available cell lines (rodent and human).
- Cells cultured from wildtype (genetically normal) rodents (partial replacement).
- Cultured cells from human subjects, including patients with neurodegenerative disease.
- Tissues and body fluids from taken from humanely killed rodents (partial replacement).
- Post-mortem brain tissue from human patients and control subjects.
- Computer-based analysis of the structure of potential drugs to infer how they might bind to their targets and other molecules.

Why were they not suitable?

These approaches are suitable for much of the work that we carry out. However, in order to fully evaluate novel drugs and their targets, which may have the potential to progress to studies in human volunteers, it is necessary to gain a thorough understanding of how they behave in a whole animal.

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?

This number is based on estimates of:

- the number of projects that we anticipate running
- the expected number of studies to validate and test potential drugs for each project on a separate licence which require mice to be bred on this licence
- the number of animals needed per study, using the minimum number of animals to give a statistically valid result

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

In designing experiments there are several factors that we will use to reduce unwanted variability in our data. This will reduce the number of animals needed to show that a result is not just due to chance:

- The number of animals used per treatment group will be carefully worked out using data from previous studies to carry out these calculations.
- Randomisation when assigning animals to treatment groups to avoid unwanted bias from factors like cage differences and time of treatment.
- When appropriate, use of baseline data when assigning animals to treatment groups to ensure that baseline measurements between groups do not differ.
- We have many years of experience in study design and statistics within our group and in addition we will draw on support from colleagues who are specialists in biostatistics.

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

Other steps we will take to reduce the number of animals used in our project:

- Using animals from the same colonies, or if possible, the same litters for comparison, to ensure that genetic variation between animals is kept to a minimum.
- Pilot studies will be used to determine the optimal conditions for experiments, e.g. the age at which experiments should be started in mice and the most appropriate ages for behavioural testing.
- Where possible, the same individual will carry out procedures, collect and analyse the data within a single experiment, and this person will be blind to the treatment which each animal receives.
- Wherever possible we will collect multiple samples from each experiment to avoid unnecessary repetition of studies, these include taking samples to determine drug efficacy, measure drug levels within tissues and investigate possible side effects all from the same experiment.

Downloaded: 9:35am, 14 Jan 2026

- Where possible, we will share information, biological samples and mouse strains with other researchers in the field.
- Increased use of cell-based assays and pilot studies has allowed us to reduce the number of drug targets to validate, and the number of drug-like molecules used in tests. This has allowed us to reduce the number of animals that need to be used for invasive procedures (e.g. procedures that involve dosing or blood sampling) as opposed to animals whose only procedures involve breeding with genetic modifications.

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.

When genetically altered mice are used, we will take steps to avoid harm to these animals:

- In some cases, the genetic alteration can be "switched on" by giving a drug either by injection or in the food. This ensures that any harm resulting from the genetic modification is experienced only during the experiment, rather than for the lifetime of the animal.
- Our establishment has released a comprehensive document on the use of these genetic alteration drugs, how they are administered effectively, and how to mitigate any transient adverse effects that may occur from their administration
- Genetically altered mouse models of neurodegenerative disease show a progressive worsening of symptoms with age. When using these mice we will use models with the mildest symptoms and at the earliest ages that are compatible with our scientific objectives.

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

Adult mice will be used in our project. While other, less sentient species, including flies, worms, frogs and fish are commonly used as experimental animals, mice are regarded as a good experimental substitute for humans as much of our genetics, anatomy and physiology are closely replicated in this species. Furthermore, there are existing mouse models of neurodegenerative disease which replicate many of the features of these conditions that are seen in human patients. Adult mice need to be used as the brain does not complete development until adulthood.

Some of our experiments are carried out in anaesthetised animals, and the animal is humanely killed without waking up. However, as we need to observe how drug treatments affect the way animals behave, and the time of treatment usually lasts from several hours up to several weeks, it is usually not possible to keep animals anaesthetised throughout the experiment.

Downloaded: 9:35am, 14 Jan 2026

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

Examples of refinement in our experimental procedures include the following:

All mice are acclimatised for at least one week after being brought into the animal facility, before any procedures are carried out to reduce the overall stress experienced by the animal.

Needles used for injections are used only once as they become blunt after multiple uses, causing increased pain and injury.

We use non-aversive handling techniques such as using a cardboard tube to pick up the mice, or supporting their weight with a hand, rather than picking them up unsupported by the tail which is known to cause anxiety.

Scoring sheets are used to record and monitor observations from genetically altered mice with symptoms of neurodegeneration.

One transgenic line shows a tendency to be hyperactive and run inside the cage. This behaviour can occasionally cause injury through the bedding becoming tangled around the leg of the animal. We will use a softer bedding type to prevent injury. We will also investigate providing running wheels for these mice.

These mice have two genetic modifications and litters contain mice that carry no modifications, either of the single modifications or both. The mice that carry both modifications are substantially smaller than their littermates and the males sometimes suffer bullying from larger mice in the cage. If bullying occurs and we need to split cages we try to house the smaller mice together, when possible, to avoid single housing.

In transgenic lines that do show disease signs, welfare is regularly monitored. Toward the end of their lives these animals experience weight loss and we use this to monitor welfare. They are weighed at least weekly, increasing to daily as the disease signs become clear. Before weight loss reaches 15% of maximum body weight animals are humanely killed.

Substances may be dosed by oral gavage - a process requiring a flexible tubing through the mouth for delivery. The tip of the tube is dipped in a sweet solution before starting the procedure to make it more palatable for the mice to swallow.

When dosing by oral gavage, mice need to be scruffed more firmly than with other techniques to prevent them from biting through the tube. We routinely place the mice on a soft surface, such as a sponge, before scruffing them, as this reduces the possibility of bruising.

When administering drugs in the animals' diet it has been found that the texture and composition of the modified diet is different from the regular diet which the mice usually eat. This has sometimes led to aversion to the modified diet and reduced food, and drug intake. When dosing drugs in the diet, we will acclimatise the mice to the modified diet without the drug for several days before switching to the diet with the drug.

Downloaded: 9:35am, 14 Jan 2026

Tamoxifen is a drug that is often used in research to switch on or off the expression of genes in genetically modified mice. This drug causes weight loss which can last for several weeks after dosing has been completed. Animals dosed with tamoxifen are routinely given dietary supplements such as softened food, peanut butter or Nutella to prevent weight loss. Our institution's vets have written guidelines to advise on the best practices for tamoxifen use, which we follow when designing our studies.

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

PREPARE guidelines checklist for designing and planning experiments

ARRIVE guidelines to ensure reporting quality of data is optimised

LASA Guidelines for Aseptic Surgery - https://www.lasa.co.uk/current_publications

NC3Rs - https://www.nc3rs.org.uk/3rs-resources

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

Regular awareness of developments via websites of organisations such as NC3Rs, LASA.

Establishment tools and communications from internal support groups.

The Named Information Officer at our establishment is a valuable resource for 3Rs information.

Downloaded: 9:35am, 14 Jan 2026