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NON-TECHNICAL SUMMARY

Molecular mechanisms in cardiometabolic disease: breeding and maintenance of genetically altered animals

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants

Key words

Breeding, Rodents, Cardiovascular disease, Diabetes, Heart failure

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

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 maintain breeding colonies to produce genetically altered mice for projects involving cardiovascular and metabolic scientific research.

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?

Animal models remain indispensable tools to investigate the molecular causes of human disease and to identify new targets for prevention, diagnosis and treatment. The combined effects of cardiovascular disease and diabetes on human health (*cardiometabolic disease*) are of major concern currently due to increasing number of people with obesity or diabetes and more people likely to develop these diseases as they age. The reasons by which obesity or diabetes increase the risk of cardiovascular diseases are complex and incompletely understood. Genetically altered mice allow us to study the effects of individual genes in the molecular pathways which contribute to diabetes and cardiovascular disease. Carrying out this work will allow us to identify new ways of preventing and treating diabetes and cardiovascular diseases.

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

1. Provision of genetically altered animals for scientific research projects investigating the role of specific genes in cardiovascular and/or metabolic disease.

2. Maintenance of rodent colonies in high-health status for use in scientific research projects

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

The outputs will benefit scientific researchers undertaking biomedical research. Mice bred on this licence will allow researchers to study the effects of specific genes on the development of obesity, diabetes, heart and circulatory disorders. Ultimately the research enabled by these outputs may lead to the discovery of new ways of preventing, diagnosing, monitoring and treating disease in humans.

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

Mice bred under this licence will be used in experimental licences held by the applicant or collaborators covering basic and translational research into cardiometabolic disease. We strive to present our research findings at national and international scientific conferences and publish our work in high

impact scientific journals. We welcome requests for collaboration from the wider scientific community. We engage in local, national and international research groupings and consortia to share knowledge and ideas.

Species and numbers of animals expected to be used

- Mice: 18 000 animals over five years

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 genetically altered mice in scientific research because it is relatively easy to alter the DNA in mice to study the effects of particular genes. Use of a mammal enables experimental results to be relevant to humans. There is a wide range of genetically altered animals available to the research community; new genetic alterations can be created by scientific or commercial organisations as new data become available. Once a genetically altered line is created, mice are bred locally to provide animals to researchers at that institution. In many cases, mice from different genetically altered lines are bred together to form colonies with multiple genetic alterations. Breeding involves mating of adult animals. Pups are maintained at life stages from neonate to adult to provide animals for scientific research projects authorised by other licences.

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

Male and female mice will be paired and allowed to breed to generate genetically altered pups. In most cases breeding also generates non-genetically altered pups which are used as controls. The presence of altered genes in pups will be determined by analysing a small piece of ear or tail. Animals will be maintained using standard husbandry procedures until they are transferred to other projects or used to replace breeding stock. Animals will be periodically visually inspected and weighed. Animals which are not used for other projects or breeding will be humanely killed.

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

Sampling of ear or tail may cause transient pain to the animal.

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 work will be of sub-threshold or mild severity limit with no suffering which is more that mild or transient.

The genetic alterations we plan to study are not known to cause harm or suffering to animals. However, when new genetically altered lines are bred or existing strains are crossed together we cannot entirely rule out the possibility of pups exhibiting clinical signs. If any new line demonstrates a phenotype which is more than mild and which develops before the animals are transferred to an experimental licence, breeding will be suspended and this will be discussed with the Home Office Inspector.

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

- Used in other projects
- 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?

This project is intended to generate genetically-altered rodents for use in other scientific research projects. Although biomedical research can often be carried out in isolated cells or tissues, in some cases the complex interactions between biological systems and the circulation can only be studied in a living animal. For example, the influence of genes on diabetes and its effects on the heart and circulation can only be studied in the intact animal. This is because diabetes affects many circulating substances including insulin, glucose and fats which all influence the heart and blood vessels. Specific rationale for the use of animals generated by this project in scientific research is provided by the licences giving authority for that experimental work.

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

We conduct many aspects of our research without the use of animals - - these include research *in silico*, in cultured cells and in tissues obtained from humans undergoing surgery.

Why were they not suitable?

The complex nature of cardio-metabolic disease involves interactions between multiple circulating and locally produced factors which cannot adequately be modelled *in vitro*. There are no suitable in vitro models for many of the cardiovascular pathologies which affect humans.

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 based on the number of experimental animals required by the licences to which this project will supply animals, taking into account breeding strategies and requirements for controls. This licence will also provide tissues for scientific research from genetically altered mice killed under Schedule 1.

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

The number of animals generated in this breeding licence is reviewed regularly and aligned with the number of animals required by the project licences it supplies. Experimental design utilises tools such as the NC3Rs experimental design assistant and is described in the licences for which this licence provides animals.

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

We design our breeding colonies and schedules to maximise generation of animals and reduce unnecessary production. This requires careful selection of which types of genetically altered animals to breed together to generate animals required for the research projects this project supplies. In a small number of cases, particularly when it is necessary to alter several genes at the same time, the required genetic alterations only occur together in a small number of offspring. In most cases, however, we can plan breeding so that all pups can be used as experimental animals or controls. We use an efficient commercial service to detect the genetic alteration in pups so that we can make early decisions on the use of animals. We use a digital animal management system to allow us to review breeding colonies on a weekly basis and hold monthly meetings with our research group to ensure the most efficient use of breeding.

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 project provides for the breeding and maintenance of genetically altered mice for use in other projects. Animals will be transferred to licences for use in other projects, used to replenish breeding

stock or will be humanely killed. Genetic alterations are of genes implicated in the molecular pathways which lead to the development of diabetes or cardiovascular disease.

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

The aims of this project can only be achieved by using mice at the ages required for breeding or for supply to other projects. Mice are the lowest order mammals in which which is feasible to readily alter genes. Although some aspects of molecular cardiovascular research can be carried out in zebrafish, it is not possible to model more complex human disorders such as diabetes, atherosclerosis or cardiac failure in zebrafish.

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

We use contemporary breeding and husbandry methods and keep ourselves updated on advances in laboratory animal husbandry and welfare. We strive to provide an environment conducive to successful breeding - for example by keeping breeding colonies in dedicated rooms and limiting access to non-essential personnel.

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

Our experimental work will follow ARRIVE and PREPARE guidance. This is covered separately in the licences providing authority for experimental work.

We will follow the NC3Rs resource for breeding and colony management written by a working group in response to returning to scientific research after the COVID-19 lockdown (https://www.nc3rs.org.uk/breeding-and-colony-management).

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

Our group stays informed through the NC3Rs website and relevant information, including the NC3Rs newsletter, is circulated within our institution by email to all personal and project licence holders. We attend local events organised by our Animal Welfare and Ethical Review Committee and information sessions on NC3Rs funding streams organised by our institution's Research & Innovation Service (last held 10th November 2020). We share best practice within our institution and have well developed interdisciplinary networks (e.g. Multidisciplinary Cardiovascular Research Centre) to facilitate this. We hold regular local user-group meetings for project licence holders at which the group receives updates on any changes to best practice or requirements.