Home Office

NON-TECHNICAL SUMMARY

The interactions of innate and adaptive immunity

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
- (c) Development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the following aims mentioned in paragraph (b)

Key words

Inflammatory bowel disease, cancer, obesity, autoimmunity, lymphocytes

Animal types	Life stages
Mice	adult, juvenile, neonate, 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 understand the interactions of innate and adaptive immune cells that cause autoimmunity, obesity and responses to cancer.

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?

To discover basic mechanisms of diseases in order to design new therapeutics and diagnostics.

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

New information, scientific publications, new biomarkers and therapeutics

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

In the short term, these outputs will contribute to better understanding of disease development and progression. In the medium to long term, patients with inflammatory bowel disease, obesity and cancer will benefit from new treatments and diagnostics.

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

National and international collaborations, conferences and publications

Species and numbers of animals expected to be used

- Mice: We estimate ~5500 mice.

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.

Complete immune system responses cannot be accurately modelled *in vitro* and addressing complex immune interactions requires the use of experimental animals. Mice are the preferred experimental animal due to their anatomical, physiological and genetic similarity to humans as well as the practical advantages of their small size, ease of maintenance, short life cycle and abundant available genetic resources. We will be using exclusively adult animals for experimental work in order to work with a fully formed and functional immune system.

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

Typically genetically altered mice will be bred specifically and placed onto a particular experimental protocol. Often mice will receive injections of substances to influence the immune system or the genetic status of the mouse or other immune interventions before proceeding to the main step of the protocol , generally the induction of an immune condition such as colitis or tumour growth or a physiological condition with immune relevance such as heart remodelling Sometimes this will involve surgical techniques such as implantation of gut tissue or heart transplant. Endoscopy may be performed to investigate development and progression of colitis. The mouse diet may also be modified.

Samples and readings may be taken throughout the experiments, these might be blood samples, physiological readings, imaging , metabolic testing or similar. Animals are generally limited to a single procedure and the duration of experiments is kept as short as possible to obtain the necessary data, mostly being a duration of weeks extending out to months only in rare cases.

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

Many mice falling under the Mild (or below) category will experience only transitory and short lived pain (such as from an injection or from ear marking) and possibly no adverse effects at all. Mice falling under the moderate category may experience pain and weight loss , for example while undergoing colitis protocols , tumour growth under tumour protocols or potentially pain under surgical protocols (i.e heart graft, implantation of Osmotic minipumps or telemeters). Mice undergoing Immune depletion may be treated with radiation leading to sickness leading to lethargy, inappetence, diarrhoea and weight loss. Adverse effects are strictly controlled for all protocols with humane endpoints established to minimise suffering at all stages , duration of any experimental protocols likely to cause adverse effects is kept to the minimum required for experimental validity.

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)?

We expect animals to fall mostly under mild severity category or below with a smaller number falling under the moderate category. Most animals bred under standard breeding protocols will be mild or below as will any animals used exclusively for tissue or used under certain protocols (Dietary manipulation, infection). Animals used under other protocols (i.e Colitis, tumour growth) will generally fall under the Moderate category . We estimate 60-70% of animals used will fall under the Mild category or below with the remainder being Moderate.

What will happen to animals at the end of 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?

There are currently no lab techniques that can accurately simulate the entire immune system and this means that animals are required for this kind of research. Replacement opportunities such as organoid/3D organ culture have been investigated by the lab and have been used to simulate aspects of the gut immune environment and may be used to replace animals under some circumstances. Further replacement technologies such as organ on a chip (chips with engineered or natural tissue designed to mimic animal physiology) are becoming increasingly advanced and may in the future allow more complete simulation of the immune system.

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

Our group is active in attempting to use lab based tests to simulate various individual aspects of the immune system where possible in order to try and minimise the requirement to use animals. We make use of human tissue and cell lines where possible and appropriate. The lab has made use of and developed protocols for organoid and 3d cell culture that allow simulation of some aspects of the gut immune system allowing potential replacement of animals for some experimental work.

Why were they not suitable?

It is not currently possible to reproduce the complexity of a complete immune system with laboratory cell line based approaches or with tissue in vitro (either human or mouse). Human material is also much less readily available and does not have the genetic flexibility of mouse models.

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?

Based on usage of current protocols that we propose to continue using and also by experience of the models and techniques used. We have a good understanding of the type and magnitude of the results we expect and therefore the size of experimental group and number of repeats needed to obtain biologically significant results.

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

We have utilised the NC3R's Experimental Design Assistant as well as only performing experiments that we know from experience give the clearest results, thereby reducing the need for experimental repeats and reducing the number of animals required.

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

We are committed to maximising the amount of experimental information we obtain from each individual experimental animal, enabling us to hopefully minimise usage. We routinely use single strains of mouse in multiple research areas, use multiple organs from the same mouse and share tissue across multiple users and experiments wherever possible in order to keep animal usage down. We are also trying to minimise the amount mice we breed for each research area by using efficient breeding and cryopreserving lines that are no longer in immediate use, thus reducing the need to breed animals purely to maintain lines (i.e "tick-over" colonies). Mouse numbers can be viewed in real time with use of online stock management allowing better control of numbers.

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 be breeding genetically altered mice for use on the project and breeding protocols do not cause any lasting distress or suffering to animals with any discomfort being associated with identification marking and being strictly temporary. Experimental protocols are primarily models of human disease (colitis, cancer, heart disease, infection etc) and are planned as to cause the minimum pain, suffering and distress while still delivering experimental data. Each protocol has strict humane endpoints and monitoring to ensure that animals do not suffer unduly.

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

Mice are the preferred species for immunological research , suffering from many of the same diseases as humans for the same genetic reasons. They are also easily genetically manipulated allowing direct

investigation of genes of interest. Mice also available inbred as to be genetically near identical which produces less variation in results and more accurate and useful disease data. From a practical standpoint they are also small and easy to house with a short life span and fast life cycle making them a costs effective research tool. Mice are one of the most common experimental animals and are generally considered less sentient than other species that may be used for research (i.e dogs, cats, primates). Adult animals are used as the nature of the protocols generally involve a period of progression over days/weeks and so use of immature life stages is not possible nor is use of animals that have been terminally anaesthetised.

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

All procedures include monitoring of animal health and condition and post operative care and pain management we believe appropriate but we will make changes as required should any regime prove to be inadequate or as suggested by animal welfare staff. Any mice that are immunosupressed due to genetic status or due to experimental treatment will be maintained in a barrier environment to limit exposure to infection. We have previously made adjustments to wording of the animal licence as well as to procedures based on observation and advice and we would see this as an ongoing process.

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

We will look to follow any published refinement guidance from bodies such as NC3Rs that is relevant to our protocols as well as following and implementing any changes suggested by animal welfare staff (NACWO, NTCO etc) or communicated to us through official channels (The Home Office). Examples of best practice guidelines informing animal use would be Guidelines for the welfare and use of animals in cancer research | British Journal of Cancer, Blood sampling:Mouse (NC3R) and mouse handling (NC3R).

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

We will follow advice from animal welfare staff at our institution regarding any 3Rs advances or improvements to techniques and ways of working. We are in regular contact with the NACWO (Named animal care and welfare officer) and NTCO/NIO (Named training and competency officer/Named information officer) and regularly pass detailed experimental plans to them for approval and comments. Animal users are encouraged to take advantage of the specific 3Rs information available on establishment webpages and also take note of communication, webinars and training offered by NC3Rs (National centre for the replacement, refinement and reduction of animals in research).