Home Office

NON-TECHNICAL SUMMARY

Development and function of the immune system

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Immune system, Signal transduction, Lymphocytes

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

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?

We aim to understand the biochemical processes within immune cells that control their development, activation, survival, migration, differentiation and function.

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?

The immune system is essential for protection from infection by pathogens. An insufficient immune response will cause humans to succumb to infectious disease, whereas an over-active immune response can result in immune pathology during infections which can be a significant cause of morbidity and mortality. Furthermore, over-activity of the immune system to innocuous stimuli results in autoimmunity, again with significant adverse health consequences. Understanding how immune cells function and are regulated is critical basic research that will underpin development of more effective therapies to support or suppress the immune system when it underperforms or overreacts.

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

The main outputs of this work will be knowledge about how biochemical processes within immune cells control their development, activation, survival, migration, differentiation and function. These will be published in peer-reviewed journals, and the publications will always be open-access and thus available to all to read for free.

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

The immediate beneficiaries of this work will be other academic researchers studying similar biochemical processes that regulate immune cell function. More broadly, it will benefit immunologists studying how the immune system responds to challenges and how autoimmunity develops. Most importantly, in the long-term, our work will provide the basis for the design of rational therapies that can modulate immune system function, which could be applied for the treatment of autoimmunity, immune-deficiency and immune pathology caused by over-exuberant immune reaction to pathogens.

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

The main outputs from the work will be published in peer-reviewed journals, and the publications will always be open-access and thus available to all to read for free. We will also communicate our work through presentations, by giving seminars at other institutions or through seminars or poster presentations at conferences. Unsuccessful approaches will be discussed openly in appropriate venues, for example at internal meetings. We have an extensive track record of collaboration, helping other groups with more limited experience in these areas of research. We will continue to support such collaborative work.

Species and numbers of animals expected to be used

- Mice: 63000

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 the animal of choice for these studies because, like humans, they are mammals and thus their immune system is closely related to the human immune system. In addition, the immune system of mice has been studied more extensively that that of any other mammal, and huge numbers of reagents are available. Most of the animals studied will be adults, but some work on the development of the immune system will be carried out using embryos, neonates or juveniles.

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

The large majority of the animals in this project will be bred in order to generate genetically altered mice and will have no further procedures done to them. These mice will be analysed once they reach adulthood by taking tissues from them for analysis in vitro once they have been killed. For some mice they will be immunised and their immune response will be studied, which may involve taking blood at several time points. In all cases much of the analysis will be done on tissue taken from the mice after they have been killed. Typical experiments may last a month, with the mice immunised at the start, bled once a week for 4 weeks and then killed for final analysis.

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

Most animals will suffer no adverse effects. A minority of animals will be injected with cells or substances to study the immune system. This will cause transient pain but no lasting harm. A small number of mice will be given viral pathogens which will cause moderate clinical symptoms.

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)?

Mild – 95%

Moderate – 5%

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?

It is not possible to comprehensively study the immune system outside the living organism, since its function depends on complex interactions between many different types of cells located in different tissues of the animal.

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

It is possible to mimic some aspects of how immune cells behave using established cell lines, however this is very limited. Indeed, such in vitro approaches work best using immune cells taken directly from animals.

Why were they not suitable?

Established cell lines are not able to replicate the behaviour of normal immune cells.

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?

The estimate is based on our current experience of carrying out similar studies under our current project licence.

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

The efficiency of animal usage will be maximised by careful control of breeding to meet research needs with respect to numbers, phenotypic uniformity and health. This has been greatly facilitated by a custom-built mouse database in which every breeding pair and every mouse born are recorded and through which we can readily monitor the numbers of mice we hold. Many experiments will require homozygous mutant animals. Littermates of these that are heterozygous or wild type will be used as age- and gender-matched controls. This allows optimal use of mouse numbers generated as well as being best scientific practice for the study of genetic alterations.

The experimental design is always based on using the smallest number of animals that are sufficient to answer the question being posed. We expect, from experience, that 6-8 animals per treatment group should be sufficient to obtain statistically robust results. For most of the quantitative experiments,

sample sizes may be set using power analysis, generally using a significance level of 5%, a power of 80%, and a difference between groups of 20%. Otherwise, we will use the minimum number of animals to provide an adequate description, generally on the basis of previous experience (ours, or from the literature).

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

Breeding strategies are always set up to maximise the number of useful mice from each litter. Wherever possible we will use multiple tissues from every animal, in order to maximise the data obtained from each mouse. Cryopreservation of sperm or embryos will be used to preserve mouse strains, thereby obviating the need for continuous breeding and thus minimizing numbers of mice used.

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 use mice since these are the mammal with the best studied immune system. Most of the work will be carried out using tissues from genetically altered moue strains analysed in vitro. Only a minority of the work will require further procedural work, such as immunisation. Where immunisation is needed, the methods to be preferentially used will be ones where there is no lasting harm to the animal, e.g. immunisation with model antigens.

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

Mice are the animal of choice for these studies because, like humans, they are mammals and thus their immune system is closely related to the human immune system. In addition, the immune system of mice has been studied more extensively that that of any other mammal, and huge numbers of reagents are available.

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

We will always choose procedures that cause the least amount of harm. Animals undergoing procedures will be carefully monitored for signs of any impairment of welfare and, in rare cases, if required will be provided with pain relief.

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

Publications from the NC3Rs and the Institute for Animal Technology, as well as relevant articles in scientific journals.

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

We stay up to date via regular communication with animal facility staff at the host establishment, other scientists in our fields, via e-mail and other updates and publications from, and occasional attendance at meetings held by, the NC3Rs, the Institute for Animal Technology, and the International Society for Transgenic Technology, and through regular visits to their websites:

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

https://www.transtechsociety.org/

https://www.iat.org.uk/