Home Office

NON-TECHNICAL SUMMARY

Mechanisms controlling immune cell killing

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

No answer provided

Animal types	Life stages
Mice	adult, 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?

The aim of this project is to understand the molecular mechanisms controlling killer cells of the immune system.

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?

Killer cells of the immune system play a critical role in defending the body against cancer and viral infections. Understanding the mechanisms that control killing by these cells will improve the design of new immunotherapies.

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

We will provide new information on pathways that are required by killer cells of the immune system. We will publish our findings in peer-reviewed, open-access journals. Findings will be presented to the scientific community at conferences and to the wider lay-audience via outreach activities including videos available on the internet.

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

In the short term the scientific community will benefit from new information about pathways required for killer cells of the immune system. Given the important role that killer cells now play in new immunotherapies the knowledge gained in this study should also improve cancer treatment.

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

We will disseminate our research output via collaboration with other scientists, scientific publications, presentations at conferences and via public engagement.

Species and numbers of animals expected to be used

- Mice: 3400

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.

Adult mice are required to generate and preserve new genetically altered lines. Adult mice enable us to generate the greatest number of mature killer cells per mouse, and use fewer mice.

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

They will be killed using a schedule 1 procedure. These mice may also be used to generate new genetically altered lines, to cryopreserve these lines and to rederive existing lines into high health animal units.

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

Genetically modified animals used are not expected to exhibit any adverse effects. Animals are monitored every day and will be immediately killed by a Schedule 1 method if they exhibit any adverse effects.

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)?

No adverse effects are expected.

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

- Kept alive

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?

The parallels between mouse and human are well understood and mice are known to provide excellent models of human disease. This allows us to study mutations that cannot be studied in man and generate results that are directly relevant to humans.

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

Human cell lines can sometimes be used as an alternative.

Why were they not suitable?

Very few human cell lines are available to study the function of the immune 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?

In the last year we have used just under 600 mice; thus we estimate we will use 3000 mice over the next 5 years.

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

The use of mice expressing a single T cell receptor (T cell receptor defined mice) to activate killer cells permits the generation of 20 fold more cells per mouse. In this way the overall number of mice required is greatly reduced.

We also include a protocol for embryo derivation so that we can cross gene deleted mice to T cell receptor defined mice. This process means that fewer generations of mice have to be bred to achieve this cross, and hence reduces the number of mice 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 have optimised culture conditions to generate and maintain killer cells in culture. We have also optimised gene deletion in cells in culture that should reduce the number of gene deletion mice required.

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 genetically modified mouse strains that do not develop any adverse effects.

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

Mice provide the best defined model of a vertebrate immune system. The parallels between mouse and human are well understood and mice provide excellent models for human disease. In this project we

only use animals to produce the cells required for experiments that we conduct in dishes in the laboratory. No animals are used in experiments, just their cells and tissues.

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

We continue to advance the use of improved in vitro cell culture, genetic manipulation and human cell lines as viable alternatives.

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

The department provides continually updated guidance on experimental refinements. Use of the website from the NC3Rs (https://www.nc3rs.org.uk) and LASA (Laboratory Animal Science Association) will also be made.

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

We constantly review methods for replacement, reduction and refinement provided by the scientific literature and our support team within the facility, attending workshops to stay up to date.