Home Office

NON-TECHNICAL SUMMARY

Mechanisms of activation of unconventional T cells

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

lymphocyte, infection, inflammation

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

Our immune system is composed of many different immune cells that function together in a coordinated fashion to protect us from disease. Immune cells are very dynamic and constantly patrol the body looking for infectious virus and bacteria. Consequently, the correct location of immune cells in the body

(being in the right place at the right time) is extremely important for them to be able to efficiently find and destroy invading pathogens. Although our immune cells are central for protection, when their functions are dysregulatedthey can cause inflammatory and autoimmune diseases such as arthritis, inflammatory bowel disease, psoriasis or diabetes.

Our research focuses on a specific family of immune cells – so called unconventional T cells - which are important in fighting infection but can also participate in the induction of autoimmune diseases. However, how the activation and function of unconventional T cells is controlled remains unknown. Our research aims to understand how, where and when activation signals are delivered to unconventional T cells and which are the consequences for health when immune responses are dysregulated.

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.

What are the potential benefits that will derive from this project?

Understanding the mechanisms and signals controlling immune cell activation and function is critical to design novel vaccination and immuno-therapeutic strategies to protect us from disease. Thus, the questions addressed in our studies are clinically relevant and the mechanisms identified in our studies will be validated in the future with samples from patients with inflammatory and infectious diseases. The data generated by this project not only will help our understanding of immune cell biology but also it will inform further research to exploit the targeted manipulation of specific immune cell subsets for therapy of various disorders.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

In our studies we will use mice as a model, since the mouse immune system closely resembles the human one, and many tools to analyse the murine immune populations are available. We estimate that we may use approximately 1500 mice/year for 5 years (7500 in total).

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

Mice will be bred to generate specific combinations of mutations of mild severity. The majority of our mice will be mildly immune-deficient, but we don’t expect them to present any signs of disease while housed in our facilities.
We will study the immune system in our mice during infection or inflammation. We may infect mice with

virus or bacteria which may cause disease. Our protocols have been designed to minimise suffering to the mice. Mice may experience symptoms similar to those of humans during infection, but normally mice will clear the infection on their own.
We have avoided techniques that might cause unnecessary discomfort to provide the information required. Animals will be anaesthetized for procedures expected to cause temporary pain and they will be carefully monitored during and after experiments.
All animals will be monitored closely and will be humanely killed if unexpected ill health occurs, if severity limits are approached or if scientific objectives have been attained.

Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

While valuable information about immune cell function has been obtained *in vitro*(by the use of cell lines), the understanding of the cellular interactions controlling the activation of immune cells in the tissues requires the use of living animals. The immune system is a complex network of different cell types that interact at specific locations and times. These cellular interactions can only be explored to a very limited extent in vitro, since the tissue/organ environment greatly influences their outcome. Therefore, the induction of immune responses with its spatial and temporal requirements can only be explored in its entirety in an intact organism.

Reduction

Explain how you will assure the use of minimum numbers of animals.

We will collect as much evidence as possible from current literature, and perform in vitro assays whenever possible before testing our hypothesis in vivo.

The breeding of transgenic animals will be reduced through collaborative access to strains.

Animal numbers used for experiments will be minimised by careful experimental design (power calculations); limitation of other variables (e.g. use of inbred strains in specific pathogen-free conditions); longitudinal monitoring; and by the employment of routinely-used protocols that work reproducibly

Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

The mouse is the ideal organism for these investigations for a variety of reasons: (a) the parallels between mouse and human immune system are well understood; (b) mouse models of immune

diseases are well established and widely used; (c) specific reagents are widely available.

All mouse models used will be assessed such that we use the minimum severity in terms of infection or inflammation burden. Commonly, these protocols are already well established and they induce only minimal discomfort. These models are generally well tolerated in most mouse strains but in all cases clear end points will be set so that any mouse displaying more than moderate discomfort will be killed.