Home Office

NON-TECHNICAL SUMMARY

Mechanisms of interaction between neutrophils and T cells

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.

Key words

T cells, neutrophils, inflammation, IL-17

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?

T cells are a subset of white blood cell which generates in the thymus and which circulates the body through the blood and lymph nodes. T cells are critical for clearing infections, but can also induce damage to host tissue, if they are activated in the wrong place or at the wrong time. For example, the subset of T cells known as Th17 are vital for clearing fungal infections, but can also induce multiple sclerosis if they are activated in the central nervous system.

T cells interact with lots of other cells in the body; however, we do not know much about how and where they interact with neutrophils, another type of blood cell which is the first responder to inflammation. We know that neutrophils and T cells are together, at the same time and place during inflammation. In the lab, we can see the cells interacting physically. However, very little work has investigated the outcome of this interaction.

This project aims to understand the role that neutrophils play in the development of T cell responses during a variety of inflammatory diseases. This will allow us to understand more deeply the pathways leading to damaging T cell activation. It may also lead to identification of new targets for therapy in these diseases.

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?

This project will lead to a deeper understanding of how T cells develop, become activated, and proliferate in tissues during inflammatory disease.

Identification of points at which neutrophils direct damaging T cell responses would enable targeting of novel therapeutics or treatment strategies for inflammatory disease.

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?

Approximately 5000 mice 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.

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?

The majority of the mice will be used in breeding of genetically modified lines.

Several inflammatory disease models will be used to assess neutrophil impact on T cell behaviour, including models of Multiple Sclerosis.

Effects on these mice in the models of MS include limp tail, paralysis, and weight loss.

All models will be of the minimum severity possible and mice will be monitored closely and strict humane endpoints implemented. Following experiments all mice will be culled humanely.

Replacement

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

We perform many experiments on human cells isolated from healthy donors; in fact, this is the majority of our work.

However, the development of immune responses is an incredibly complex chain of events, which is impossible to study *in vitro* owing to the large number of ‘unknown unknowns’. In addition, key experiments include the movement of different types of white blood cell around the body in response to triggers, and the assessment of immune responses in complex and hard to reach tissue such as the brain. This cannot be modelled in culture or removed from human patients. As such, animal experiments are necessary.

Throughout the project we will continue to seek alternatives to animal experiments.

Reduction

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

Initial experiments are performed on human and mouse cells in culture, so that hypotheses are formed without using animals.

Experiments are designed to track animals over a period of time, using repeated measures and a large number of measured outcomes and tissue collection procedures, to cut the number of animals required.

Experiments have been designed in collaboration with statistical advice in order to detect significant effects with a lower number of mice. Following initial experiments, statistical analyses will be performed in order to use the minimum number of animals possible to gain significant results.

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.

Our team, both scientific staff and animal technicians, are very experienced in handling and experimenting on animals, which will reduce stress and suffering of the animals. The unit in which the animals are kept is well-resourced and well-equipped. Advice is taken routinely from veterinary staff and all experiments are submitted first to the vets for review.

The mouse models used are extensively characterised and replicate human disease and immune processes very well. The welfare costs to the animals will be minimised by looking at early disease time points. Published data on these models means hypothesis-forming experiments are much fewer than would be required in other models. Using mice also allows many experimental measures to be assessed, owing to the enormous number of reagents available and the use of transgenic animals.

Prior to and during experiments animal health will be maintained using good breeding and handling techniques and housing in ventilated cages.

Mice will be monitored closely and assessed using a well-characterised severity score sheet. Support measures such as soft food and analgesia will be provided. And mice will be culled humanely when a humane endpoint is reached, for example a specific level of body weight loss.