Home Office

NON-TECHNICAL SUMMARY

Investigating the role of humoral immunity in tissue-specific immune responses in health and disease

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

B cells, infection, kidney, intestine, brain, cancer

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?

The immune system is the body's defence system, protecting it from infections and cancers, and helping to repair damage to tissues. It was previously thought that immune cells mostly lived in the blood and 'professional immune organs' such as the lymph node and spleen. However, recent studies show that some immune cells permanently live in different organs, like the kidney.

Our aim is to investigate one part of the immune system – 'humoral immunity'. This includes immune cells called B cells, which become plasma cells and produce soluble defence molecules called antibodies. We want to find out how many and what sort of B and plasma cells live in different tissues, whether they play a part in responses to local infection or tissue damage, and if this changes with age. The tissues we are particularly interested in are the intestine, the kidneys and bladder, and the brain, including the membranes that line the brain, the meninges. We also want to look at how these cells change when a tissue becomes cancerous.

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 improve our understanding of the role of tissue B cells and plasma cells in infection and inflammation in different parts of the body. This includes the intestine, providing information that can be used to develop treatments for gut inflammation (conditions like inflammatory bowel disease). These diseases are currently increasing in prevalence and some patients do not respond to standard therapy.
Our work on kidney and bladder immunity will help identify strategies for the prevention and treatment for urinary tract infection, kidney injury and kidney transplant rejection. This will help prevent people from getting kidney failure and make kidney transplants last longer, with important benefits; dialysis accounts for 2% of total NHS spending and transplantation restores patient independence and allows return to work.
There is currently little information about the cells in the brain linings, and our work will be relevant to understanding and finding treatments across a broad range of brain disorders, including meningitis, mood disorders and neurodegenerative diseases such as Parkinson's disease.
Finally, there is an increasing appreciation that immune responses can be harnessed to help fight cancers, but little is known about the part of the immune system that we are studying. Our project will begin to address this knowledge gap.

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?

Species- Mouse.
10000 over 5 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?

Some animals will undergo an immunisation – this is just like receiving a vaccine, and then tissue immune cells will be assessed by taking organs following killing by a humane method.
In other cases we will use infection models where mice are given a kidney or bladder infection or a gut infection to determine how B cells and antibodies affect these infections. For some experiments we will place some tumour cells underneath the skin and assess whether B cells and antibodies affect the ability of tumour cells to grow. In all cases, the mice will be carefully monitored for adverse effects such as weight loss, diarrhoea, abnormal kidney function or the tumour size measured regularly, so that we can make sure that experiments are terminated before the disease becomes too severe. Blood, urine, and faecal samples may be collected and we may also perform scans using special microscopes whilst the animal is anaesthetised. In these cases the mouse is put under deep anaesthesia and carefully monitored.
In all cases, animals will be humanely killed at the end of their breeding lifespan or at the end of experiments and following death tissues will be further processed for detailed investigations.

Replacement

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

We will carry out many parts of our research using cells grown outside of the animal in tissue culture to minimise animal use.

We have obtained ethical permission to use human cells for some studies and cells from human organ donors that have given consent for their tissues to be used for research, so we can investigate immune cells in multiple organs including spleen, kidney, bladder and liver.

However, although these approaches can provide some useful information, they cannot accurately model an immune response in a body, which is complex and requires a coordinated action from many different immune cell types. This response takes place within specific tissues, and is influenced by these differing environments. The complex interactions between immune cells, the environment of different organs, and a whole body immune response cannot be recapitulated using tissue culture methods hence the need for animal models.

Reduction

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

When designing the experiments statistical analyses ensure the use of minimum number of mice per group.

We have obtained mouse strains that have fluorescent immune cells that we can scan, something that is difficult to achieve using labelling techniques. This will limit the number of mice required for these studies. In addition, numerous cells can be imaged at once, generating a large amount of data and information per animal, which will also limit the overall number of mice required.

To avoid breeding new mouse strains we will investigate specific immune cells that are labelled. We will provide any excess mice generated by our breeding programme to a number of other researchers avoiding duplication where other groups breed the same strain.

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.

We will be using genetically modified mice that have been bred for our research, and have alterations in the amount of B cells, the immune cells which we are interested in. This maximises the quality of experimental data generated, minimising the numbers of animal required.

In order to carry out imaging studies, we have imported fluorescent reporter mice made by expert imaging laboratories. These provide the best possible way of seeing specific immune cells as they have fluorescent markers which tag specific cells on our microscopes. This means there is a large amount of data that can be generated from a single experiment. The mice are kept deeply anaesthetised for the full duration of the imaging, but this technique allows us to magnify and image in real time the interactions of individual cells in the animal.

We minimise suffering via careful and skilful handling of the animals, use of the smallest possible size of needles, minimal numbers and frequency of repeated steps of the experiments. We constantly refine our protocols to ensure that the least amount of harm is caused to the animals during protocols whilst trying to gather the most amount of scientific data. Where possible we store samples to archive for future use.

All animals undergoing a procedure will be carefully monitored for signs of distress thereafter, and treated appropriately or humanely killed by an authorised method to minimise any suffering.