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NON-TECHNICAL SUMMARY

Cell signalling in immunity, infection and cancer

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

Immunity, Infection, Cancer, PI3K, Cell signalling

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 objectives are to study the processes that affects our susceptibility to infections and cancer.

We will perform experiments designed to improve our understanding of why mice and humans have eight versions of a particular family of enzymes called the PI3Ks. These enzymes are the targets of several new drugs used in humans and therefore it is important that we understand their physiological roles. We mainly study these in the context of immune cell development and function.

We will also use mice to study leukaemias and lymphoma. These are cancers of the immune system (white blood cells). The particular types we study are caused by uncontrolled division of a type of white blood cell called B cells. These are the cells that make antibodies. We will investigate what makes these B cells multiply to cause cancer, how one can use drugs to stop them multiplying and even kill them. We are particularly enthusiastic about studies we have imitated which may reveal how we can harness the power of our immune system to kill these B cell cancers. These studies could have important impacts on the future therapy of B cell cancers. Indeed, our work has already contributed to the development of new drugs to treat B cell cancers (Idelalisib).

We will also investigate strategies to enlist the help of the immune system against other types of cancers, focusing initially on breast cancer. We have discovered that inhibiting one of the PI3Ks, called PI3Kdelta, can elicit a potent immune response to cancer. Now we want to better understand how one can combine drugs against PI3Kdelta with other therapies for better outcomes for patients.

We have discovered an inherited primary immunodeficiency disease known to affect a few hundred patients world-wide who suffer from poor immune responses and increased risk of *Streptococcus pneumoniae*, a bacterium that is among the most common causes of pneumonia. We have generated a mouse model of this disease and we are working with pharmaceutical companies to explore how this disease can be treated. Patients with this immunodeficiency disease have greater risk of developing B cell cancers and we will characterise how these cancers arise and how they can be most effectively treated using novel therapeutic agents.

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?

The most immediate benefit of this research is improved understanding of the important role that PI3Ks play in regulating the immune response.

This knowledge may help the development of better medicines to treat patients with cancer or patients with poor immune systems.

Our research has already contributed to the development of new treatments that prolong the lives of patients with B cell leukaemia or lymphoma. We hope to further increase the utility of such drugs to treat such cancers of the immune system more effectively with fewer side effects.

We are actively extending this work to determine if PI3K inhibitors can also benefit patients with other types of cancer. The way this works is by increasing the immune-responses against these cancers. We

are working closely with clinical teams who are exploring these concepts in clinical trials involving cancer patients.

We also work on a recently discovered primary immunodeficiency. This is a rare inherited disease that causes loss of normal immune function. Patients get infections such as pneumonia which in some cases cause their lungs to stop working. Our work using a mouse model of this disease has direct impact on clinical trials. We believe the lessons we have learned from studying this rare disease may also benefit patients suffering from more common diseases, such as chronic obstructive pulmonary disease (COPD). This is a disease of the lungs, often caused by smoking or pollution. The symptoms of COPD often get worse after infection. Our research may help improve the lives of patients with COPD and we are exploring this with a major pharmaceutical company.

We work closely with clinicians and pharmaceutical companies to ensure that results we produce can be translated to human benefit where possible.

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?

We will use about 42,000 mice over a 5-year period.

Mice are the most appropriate model we can use to address our scientific aims. This is because they can be genetically modified and we have access to many lines of such genetically modified mice. Mice have immune systems that closely mimic human immune systems. We have shown that the studies we perform in mice are of immediate relevance to human diseases for which we aim to develop novel therapeutics.

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 mice bred on this licence will be maintained in ventilated cages that contain environmental enrichment, including opportunities to climb and materials used to make nests. No more than 5 weaned mice are kept per cage.

A large proportion of the mice kept on this licence are genetically modified. Most of these genetic modifications do not have a direct impact on the health or behaviour of the mice. The main exception to this is that some of the genetic modifications increase the chance of the mice developing cancer. This will affect about 5% of the mice which will be monitored regularly to ensure the mice are killed humanely before the cancer affects their well-being or normal behaviour.

About 20% of the mice will experience mild discomfort because we infect the mice with vaccines, bacteria, viruses or tumours. These are usually injected into the tail vein or under the skin. Streptococci

or flu viruses may be given by inhalation through the nose. The mice may experience transient discomfort or pain due to injections or slight fevers. Mice may also experience temporary swelling at the site of injection of a virus, which can last for 10-12 days until the infection is resolved. About 5% of the mice will experience symptoms that reduce their normal behaviour in the cages if they feel ill because of more sustained fever, shortness of breath due to lung infections, or because tumours cause local pain. The size of the tumour is monitored and will not exceed a pre-defined limit and will not cause the mouse to alter its normal behaviour. Some lymphoma cells can migrate and establish themselves in the central nervous system (this is also an important clinical problem). Mice showing early signs of paralysis as a consequence of CNS lymphoma will be killed humanely.

Some mice are given anaesthetics. This is usually administered by inhalation. Mice recover quickly and resume normal behaviour 10-5 minutes after being anaesthetised. Some mice may be given injected anaesthetics by injection. Such mice take longer to recover, will be kept warm and under observation until they resume normal behaviour (normally within 1-2 hours).

Careful monitoring will ensure that mice are killed humanely once they start experiencing such adverse effects so that any suffering is kept to a minimum. All mice will be killed humanely by the end of the experiment and tissues taken for analysis. No mice will ever be used for a second set of experiments.

Replacement

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

Most of our studies investigate immune responses mediated by white blood cells called T cells and B cells. These are the types of immune responses that are responsible for the protective effects of vaccines. Non-vertebrate animals do not have B cells or T cells. In some studies, we use T cells or B cells isolated from human blood. However, most of the experiments described in this licence cannot be done using human volunteers or with donated blood or tissues from cadavers. In particular, we depend on using genetically modified organisms so that we can study the function of particular genes. We also need to access tissues and immune cells during infections and from tumours.

Reduction

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

The most important method to reduce animal numbers used is through careful planning and monitoring of the mice we breed so that we do not produce more than we need for our experiments. We use an advanced database to manage the breeding pairs and to maximise the use we get out of each litter.

We have developed cell culture techniques that allow us to do many experiments in the laboratory with cells taken from mice in the past and archived in a freezer. Therefore, one mouse can provide tissue we continue to investigate, in some cases for several years after we had to kill the mouse.

The adoptive transfer of immune cells is a mild intervention that enables us to evaluate how genetic modification of T cells affect their trafficking to different organs and physiological responses. This method can sometimes circumvent the generation of additional genetically modified mice and more complex breeding strategies and hence may lead to a reduction in the number of mice bred for experimental purposes.

Each experiment is designed to use the minimal number of animals per group that can provide statistically meaningful results.

We never re-use animals for different experiments.

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 an ideal species as they have very similar immune systems to humans and most of the genes and proteins that control human immune cells are also found in mice. Therefore, if we wish to understand how a particular gene affects immune function in humans, mice can often provide a reliable answer, even though some of the finer details may differ.

Each experiment described in this licence has been designed to minimise harm to animals while maximising the data we can collect and analyse. This is achieved by choosing procedures that cause the least harm (often based on what is used for human patients) and by having very clearly explained end-points, that is symptoms that would cause a mouse to be removed from a study and killed humanely. For instance, we increasingly use vaccines commonly used in children and the elderly to study the immune system in mice, rather than more traditional reagents (one is called Freund's adjuvant, a mixture of oil and bacteria), which cause inflammation.

In addition to this licence we will generate observation forms and standard operating procedures which will help everyone involved ensure that animal welfare is maximised while pain and suffering are minimised. Mice are kept in cages that allow them to move about freely, climb, dig and interact socially with each other. The mice have unrestricted access to water and food. We try to minimise direct handling of the mice and will for instance use paper rolls they can climb into when moving them from cage to cage.