Home Office

NON-TECHNICAL SUMMARY

Retrovirus-immune system interaction in mice

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.
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants.

Key words

Retroviruses, immunity, cancer, T cells

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?

Infectious diseases are a leading cause of death worldwide, and are increasing in almost every nation. Infection also directly cause 1 in every 5 cancers. They are also among the biggest disablers. Protection against infection by viruses and other pathogens as well as the efficacy of vaccination crucially depend on appropriate activation of the immune system, a complex and vital network of cells and organs that fights invading pathogens. An understanding of these molecular pathways is essential for the design of vaccines for prevention and intervention in viral infections and cancer.

Our aim is to study the various molecules and mechanisms, which trigger the immune response to achieve long-term protection from infectious retroviruses or endogenous retroviruses expressed in cancer cells, with minimum pathology, and the broader interaction between retroviruses, both endogenous and exogenous, with their hosts.

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 results of the research carried out under this project will be disseminated through publication in high quality peer reviewed journals and at meetings. The potential benefit is an improved understanding of the immune response to retroviruses and cancer. The knowledge gained from the vaccine experiments may be directly transferable to human vaccine studies or trials either through our institution or by other interested parties. The studies on immunopathology may lead to a better understanding of the molecules and cells contributing to pathogenesis. This knowledge may help in the design of intervention therapies in clinical therapeutics in immune pathologies.

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?

To achieve the objectives outlined above we propose to use the laboratory mouse as the model organism. We estimate that we will be using approximately 12,000 mice per year, the majority of which (~70%) will only be used for breeding.

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?

We are proposing to use appropriate mouse models for clinically-relevant viral infections and cancer, in which the parameters of protective immunity can be studies and tested. Mouse models for infection with retroviruses will be studied in detail. In addition, genetic alteration of specific genes will reveal their

precise role in the response infection, autoimmunity or cancer. The most acute signs we expect to see in the experimental animals will be the result of tumour development. However, this is expected only in a small minority (~10%) of all the mice that will be used in this programme. Common to pathogenic murine retroviral infection or cancer models is the assessment of pathogenicity. This will be assessed most frequently as morbidity, which is quantifying changes in physiological parameters relevant to each type of infection or cancer and associated clinical. When clinical symptoms reach a predefined and closely monitored level or the physiological parameters reach the predefined values, mice will be humanely killed by a Schedule 1 method.

Replacement

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

Initially, the role of different mediators and compounds, which can affect the induction of an immune response to and/or growth of a pathogen, will be determined in *in vitro* studies. Ultimately, however, the immunological and immunopathological investigations, and particularly vaccine and antimicrobial effectiveness and autoimmune pathologies, cannot be carried out without the use of animals, since the host's immune system cannot be entirely mimicked by any *in vitro* assay. Furthermore, although all compounds will be selected for *in vivo* testing based on evidence of activity in relevant *in vitro* assays, this cannot replace the *in vivo* tests under the physiological conditions of an infection, as potent *in vitro* activity might not translate into an *in vivo* activity.

Reduction

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

The design of quantitative experiments will be based on our extensive prior experience with the animal models proposed in this application and will additionally be tested against power and sample size algorithms. This combination will allow us to calculate with accuracy the minimum number of mice required to obtain a scientifically meaningful result. Using too few mice would lead to inconclusive results.

Moreover, results will be reported according to ARRIVE (Reporting of In Vivo Experiments) guidelines published by the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (PLoS Biol 8(6): e1000412. doi:10.1371/journal.pbio.1000412).

The use of dedicated computer databases for mouse breeding and management has been implemented at our Institute. This allows us to carefully monitor the mouse breeding programme and also share mice with selected genetic traits between investigators so that duplication is avoided. Cryopreservation of gametes, embryos, tissues and cells is also routine at our Institute and will ensure that the minimum number of mice is bred.

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 best-characterised model for these studies, with many features applicable to human infection. Their immune responses are well defined and the technology enabling sophisticated manipulations of the haematopoietic and immune system is highly developed. Mouse transgenic and knockout techniques are well established; mice have a relatively short generation time; its haematopoietic system has been extensively studied and, in addition to the accumulated knowledge, there exists a vast array of reagents that facilitate the studies to a level unknown for many other organisms. To our knowledge no other species of lesser sentience can fulfil the requirements of this project to the same extent as the mouse.

In our experiments, specific end-points will be used to monitor the effect of infection on physiology, instead of induction of pathology, and we will go to great lengths to minimise the possibility of severe pathology. This will be achieved by close monitoring of symptoms and physiological parameters during the course of the infection. We will use genetically-modified micro-organisms as challenge strains in order to take advantage of reporter signals – luminescence or fluorescence, for example – to monitor the course of infection and potential dissemination to different organs with non-invasive techniques.