Home Office

NON-TECHNICAL SUMMARY

Identification of determinants of pathology and protection in respiratory infections

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

Lung infection, immune response, tissue damage, epithelium, repair

Retrospective assessment

> The Secretary of State has determined that a retrospective assessment of this licence is required, and should be submitted within 6 months of the licence's revocation date.

Reason for retrospective assessment

This may include reasons from previous versions of this licence.

- Contains severe procedures
- Required at inspector’s discretion

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 respiratory infections like influenza and tuberculosis are among the biggest killers. Influenza kills up to half a million people in a normal flu season, and in historic pandemics, up to 50 million people were killed by influenza infection. Lung damage can be caused by the infectious pathogens directly, or by the activation of the body's immune response that should actually be protective. We try to understand what decides whether the immune response protects or damages the lung. We use the most advanced cell culture systems to study effects of influenza virus infection or novel CoV infection on lung epithelia, with the aim of directing and focussing our experiments in live animals to keep animal numbers down.

A retrospective assessment of these aims will be due by 25 October 2023

The PPL holder will be required to disclose:

- Is there a plan for this work to continue under another licence?
- Did the project achieve it's aims and if not, why not?

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?

Given the huge clinical problem, understanding lung infections better is the first step to improving their outcome. We concentrate on two aspects: Which parts of the immune response cause lung damage rather than combat the infection? What factors hinder the lung repair that is crucial for recovery at the end of a lung infection? Answers to these questions will pave the way for novel therapies, to improve the course of infections in humans.

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 our objectives we propose to use the laboratory mouse as the model organism, since infections in mice mirror human infections well, and many tools to analyse the mouse immune system are available. We estimate that we will be using approximately 10,000 mice per year, a large fraction of which (~30%) will only be used for tissue sampling. We use advanced statistical methods and breeding schemes to make the most efficient use of our mouse breeding colonies.

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?

Many but not all mice used in this project will be infected, and the mice will experience symptoms similar to those humans have during lung infections. Common to all infectious models is the assessment of virulence or pathogenicity. This will be assessed most frequently as morbidity, which is quantifying changes in physiological parameters relevant to each type of infection and clinical symptoms associated with all types of infection. Many of the pathogens proposed to be used in the project can cause disease, however, every effort will be made to limit infection-associated pathology to the absolute minimum required for answering our scientific questions. As COVID-19 disease and related infection models are novel, the monitoring for adverse events and severity are modelled along our experience in influenza infection, with input from the scientific literature. We found so far that clinical scoring in combination with weight loss monitoring appears to predict the severity well (e.g. symptom scoring correlates to initial dose of virus infection, typical markers for severe disease in patients are found in our severe but less so in our moderate infections), and we are constantly revising these parameters to stay as close as possible to the human disease (e.g. mice present with symptoms of disease including lack of activity, lack of appetite, weight loss and breathing difficulties) and at the same time provide maximum animal welfare while being able to answer our scientific questions regarding the determinants of severity and treatments to improve outcome of COVID-19 disease.

A retrospective assessment of these predicted harms will be due by 25 October 2023

The PPL holder will be required to disclose:

- What harms were caused to the animals, how severe were those harms and how many animals were affected?

Replacement

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

We try to do as much preliminary work as possible in tissue culture, even though the many parallel processes happening during a lung infection cannot be reproduced in culture entirely. We are constantly working on improving the tissue culture systems to make them more predictive of what happens in an infected organism.

A retrospective assessment of replacement will be due by 25 October 2023

The PPL holder will be required to disclose:

- What, if any, non-animal alternatives were used or explored after the project started, and is there anything others can learn from your experience?

Reduction

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

Before we start working with mice, we test most candidate compounds and mechanisms in tissue culture, as far as this is possible. This allows us to test in mice only the most promising and potent molecules, and to investigate only the mechanisms we found to be in action in tissue culture. This greatly reduces animal numbers. We also aim to calculate the smallest number of animals required to obtain a clear answer from our mouse experiments.

A retrospective assessment of reduction will be due by by 25 October 2023

The PPL holder will be required to disclose:

- How did you minimise the numbers of animals used on your project and is there anything others can learn from your experience?

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 infection studies, with many features that resemble human infection. Their immune responses are well defined and the technology allowing analysis and manipulation of the immune system is highly developed. 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 as well as the mouse.

In our experiments, we define specific end-points 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. During the infection phase, we take a range of measures to insure the mice do not suffer more than necessary, for instance helping the body temperature stay constant and avoiding dehydration. We will use genetically-modified micro-organisms for infections 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. These and other longitudinal measurements allow to use fewer mice and obtain more robust data.

A retrospective assessment of refinement will be due by by 25 October 2023

The PPL holder will be required to disclose:

- With the knowledge you have now, could the choice of animals or model(s) used be improved for future work of this kind? During the project, how did you minimise harm to the animals?