Home Office

NON-TECHNICAL SUMMARY

Ischaemia Reperfusion Injury and Organ Transplantation

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

Transplantation, Ischaemia-reperfusion Injury, Rejection, Treatment

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?

Organ transplantation is the life-saving treatment for many diseases. Two related mechanisms of injury during organ transplantation include the damage caused by the lack of oxygen during transplantation and the immune response to the transplanted organ. The aim of this project is to study these mechanisms of injury and investigate the efficacy of targeted therapies to reduce injury and improve organ function after transplantation.

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?

Approximately 1000 patients die or are removed from that transplant waiting list every year, although this is thought to represent only a fraction of the true health burden. The main contributor to these 'avoidable' deaths are shortage of organs suitable for transplantation, compounded by premature failure of organs after transplantation. The data generated by this study is essential for conducting human clinical trials on novel therapeutic agents in transplantation. It is anticipated that this programme of work will generate new insights into mechanisms of injury during transplantation and identify new targets for therapy. Therapeutic approaches developed as part of this program will directly inform the design of clinical trials to ameliorate injury during transplantation. Moreover, many of the mechanisms of injury in transplantation are expected to be common to other diseases such as heart attacks and strokes. It is expected, therefore, that the findings from this study will also be applicable to treatment of such other conditions.

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?

Up to 6125 mice will be used over a period of 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?

The experiments in this project are designed to study the mechanisms and the treatment of organ injury in transplantation. Some animals will be used as organ or tissue donors. The removal of tissue will be under terminal anaesthesia and will therefore not cause distress to the animals. Some experiments will involve the transplantation of organs (heart or kidney) into other mice, or causing injury to organs (kidney or part of the liver) by interrupting their blood supply for short periods. These surgical techniques have been refined and optimised to ensure that, when performed successfully, the animals can make a full recovery from procedure. Animals with heart or kidney transplants are therefore not

expected to display any clinical signs. Technical failure of these complex procedures will be noted at the time of the operation and the animals will be culled under anaesthesia. If technical failures lead to adverse effects soon after recovery of the animals, the animals will be culled as soon as adverse effects are noted. Late failure of heart transplants will also not result in clinical signs. Failure of transplanted kidneys can result in gradual and slow-progression of clinical signs such as weight loss. The animals will be culled if these adverse effects are displayed. The risks of wound infection or wound dehiscence after operation are generally very low (<5%).

Animals will undergo a maximum of two invasive procedures under general anaesthesia followed by recovery. The majority (>80%) of the animals are expected to recover well from the procedures and are not expected to show signs of adverse effects that impact materially on their general well-being. No more than 20% of animals are expected to show clinical signs of a moderate severity as a result of the effects of surgery or treatment with drugs. Rarely the severity of these signs may be such that the humane end points may be reached. Mice will be killed if they show significant signs of ill health, such as weight loss, piloerection and hunched posture or inactivity. If animals display mild signs, animals may be killed if they do not improve after up to 24 hours of observation.

Replacement

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

The definitive study of mechanisms and therapies to reduce injury during organ transplantation requires examination in intact animals. However, as part of this project, we are also making extensive use of fresh live tissue and organs from deceased human organ donors, to enable many of the questions to be answered as best as possible without the use of animals. Replacement of animal use with human tissues and organs are therefore a fundamental component of the proposed studies.

Reduction

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

Through the use of human tissues and organs, we will reduce the number of animals used to achieve the aims and objectives of this experimental programme. The experiments are design to reduce experimental bias and improve the validity of the data generated through randomisation and systematic blinding of the experimental groups. Only therapeutic agents that have shown efficacy in vitro will be examined in vivo to reduce the number of animal experiments.

We will use multiple tissues and organs from each animal to maximise the data generated and reduce the number of animals used in the project. Tissue from culled animals will also be shared proactively with other researchers to reduce animal use by other research groups.

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 models used are optimally suited to achieve the aims and objectives of the study. We have refined the protocols and procedures for the generation and maintenance of these mice to maximise the likelihood of the success of the experiments and to minimise stress and harm to animals. The vast majority of the experiments are designed such that the animals only experience minor discomfort, and serious ill health or death is never an expected end-point.

In the heart transplant procedure, the heart from a donor animal is transplanted into the abdomen of a recipient animal. In this model, subsequent failure of the transplanted heart does not result in any ill effect in the recipient animal. Similarly, in the kidney transplant procedure, one of the recipient animal's kidneys is left intact, and only removed later if the transplanted organ is functioning. This ensures that the recipient animal does not experience adverse clinical effects even if the transplanted organ fails soon after transplantation. In both models, the health of the recipient animal is not dependent on the function of the transplanted organ. Similarly, in experiments in which the blood supply to the kidney or part of the liver is temporarily interrupted, the duration of the interruption is limited to ensure this does not lead to adverse clinical signs (but allows biochemical detection of changes in organ function). These refinements minimise adverse effects experienced by the animals, while allowing the generation of important data by the experiments.