G. NON TECHNICAL SUMMARY (NTS)

Project title: Ischaemia Reperfusion Injury and Organ Transplantation
Duration of project - years: 5
Duration of project - months: 0

Purpose of the project (as in ASPA Section 5C(3)):
(a) basic research: YES
(b) translational or applied research with one of the following aims:
   (i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their
       effects, in man, animals or plants: YES
   (ii) assessment, detection, regulation or modification of physiological conditions in man, animals or
        plants: NO
   (iii) improvement of the welfare of animals or of the production conditions for animals reared for
        agricultural purposes: NO

(c) development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs
    and feedstuffs or any other substances or products, with one of the aims mentioned in paragraph (b):
    NO
(d) protection of the natural environment in the interests of the health or welfare of man or animals:
    NO
(e) research aimed at preserving the species of animal subjected to regulated procedures as part of
    the programme of work: NO
(f) higher education or training for the acquisition, maintenance or improvement of vocational skills:
    NO
(g) forensic inquiries: NO

Keywords:
Transplantation, Ischaemia-reperfusion Injury, Rejection, Treatment

Describe the aims and objectives of the project (e.g. the scientific unknowns or
scientific/clinical needs being addressed):
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.

What are the potential benefits likely to derive from this project (how science could be advanced
or humans or animals could benefit from the 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.

What types and approximate numbers of animals do you expect to use and over what period of time?:
Up to 6125 mice will be used over a period of 5 years.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels 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 (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.

Application of the 3Rs

Replacement:
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:

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.

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at https://www.gov.uk/government/publications/government-security-classifications. Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location. All government information may be subject to an FOI request and subsequent assessment.
Refinement:

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.