Home Office

NON-TECHNICAL SUMMARY

Cell proliferation, death and cell senescence in cardiovascular disease

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

Atherosclerosis, aneurysm, cell death, Cell proliferation, Ageing

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?

Atherosclerosis is a disease that causes thickening of the arteries, and is responsible for heart attack and strokes, the commonest cause of death in the UK. Arterial aneurysms are a localised expansion of the artery that may cause rupture and sudden death in humans, and we have no current treatment for them. The primary goal of the project is to understand how cell processes such as cell death, cell proliferation and cell ageing (senescence) contribute to diseases such as atherosclerosis, formation of an aneurysm, vessel injury and vessel ageing, and to identify treatments for these diseases.

A retrospective assessment of these aims will be due by 10 December 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?

We will explore ways to reduce or increase cell death and cell ageing (senescence), or increase cell proliferation to inhibit disease progression. If we can do this we may be able to develop both new strategies and new treatments that could reduce the burden of heart attacks and strokes, and reduce aneurysm formation or progression.

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?

Mouse. Total numbers are approximately 16850 over 5 years. However, the vast majority of animals will be simply bred to get the required genotype.

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?

Most of the animals are just bred to generate the required genotype. Some of these animals are then fed a diet that leads to atherosclerosis, and / or may undergo additional procedures such as drug administration, artery surgery or bone marrow transplantation. Most of these procedures result in few adverse effects, and most protocols are no more than moderate severity, although development of a vascular aneurysm may result in a severe phenotype. At the end most animals will be killed humanely, although some mice on experimental protocols will undergo perfusion fixation under terminal anaesthesia.

A retrospective assessment of these predicted harms will be due by 10 December 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.

The research plan involves in vitro work using tissue culture techniques to understand cell death, proliferation and ageing, to determine the genes and molecules responsible, and validate against human tissues and cells. However, the complex processes involved in atherosclerosis, aneurysm formation, and vessel ageing cannot be reproduced in vitro. We therefore need animal models to mimic human disease and to test the impact of novel therapeutic strategies on disease development and complications in vivo.

A retrospective assessment of replacement will be due by 10 December 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.

The number of animals is minimised by careful experimental design according to extensive previous experience in the models, and is determined according to pre-defined and appropriate statistical analyses. We have used imaging to sequentially follow the same animal, such that each mouse is its own control for changes over time. This also markedly reduces number needed.

A retrospective assessment of reduction will be due by by 10 December 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 models have genetic alterations to make them susceptible to disease, or have over- or under-expressed genes. Most protocols are no more than moderate severity, but the aneurysm protocol could be severe, which reflects the severity of the consequences seen in humans (aortic rupture and death). In these protocols, surgery is done under general anaesthesia, so the animal does not suffer, and animals monitored at least every day and up to 28 days after surgery to detect any sign of cardiac failure (reduced movement, hunching, breathless at rest), aneurysm rupture or signs of limb necrosis. If this occurs, the animals will be killed by a schedule 1 protocol.

We always choose the least severe route and scheduling for the administration of substances (e.g. in drinking water/food) that still ensures a good dose of the substance in vivo, and always use anaesthetic and analgesics, where appropriate, to minimise animal suffering. For example, if a mouse is under general anaesthesia for a protocol and subsequently requires injection of a substance on the same day, it would benefit welfare to administer the substance under the same general anaesthesia – thus reducing handling post-surgery.

A retrospective assessment of refinement will be due by by 10 December 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?