Home Office

NON-TECHNICAL SUMMARY

New treatment strategies for myocardial infarction and aortic aneurysm

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

Aortic aneurysm, Marfan syndrome, Cardiac regeneration, Stem cell

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?

Blood vessel obstruction is commonly caused by Atherosclerosis - a 'furring up' of the inside of a vessel. This leads to heart attacks and loss of heart muscle, when blood flow is interrupted in the arteries supplying blood to the heart, and to strokes when blood flow to the brain is interrupted.

Alternatively, weakness of the artery wall leads to a 'ballooning' of the vessel, also known as an aortic aneurysm: devastating if this tears or bursts. Marfan syndrome is an example of this kind of disease.

Under this llicence we will:

1. Determine the origins of the cells that repair the heart following heart attack and how these cells are activated and switched on when needed.

2. Establish whether stem cell-derived cells can be used to regenerate the damaged heart muscle following a heart attack.

3. Identify the signals that trigger aneurysms in large blood vessels using human stem cells, test whether the same signals cause aneurysms in animal models of these conditions and develop new treatments for aortic aneurysm.

A retrospective assessment of these aims will be due by 28 July 2024

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?

1. Understanding how heart and blood vessels develop and their responses to injury and disease – new scientific knowledge.
2. Developing a way to regenerate injured heart muscle after a heart attack, using stem cells.
3. Identifying new treatments for aortic aneurysms.

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?

Approximately 8600 mice and 650 rats over 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?

For objective 1, genetically modified mice in which we can track heart cells will be used to identify which cells contribute to repair after a surgically induced heart attack and what genes may control this repair process. Some animals will be treated with medication to see if we can alter the repair response. For objective 2, we will try and regenerate the damage done to the heart after a surgically induced heart attack by treating rats or mice with stem cells aiming to restore heart function. For objective 3, we will use mice that develop aortic aneurysms either due to a mutation in their genes or caused surgically or by a drug treatment. The work will identify exactly how aneurysms develop and new treatments to prevent this.

The majority of animals on this licence will be under mild or moderate protocols, and suffer minimal adverse effects. However, to test and develop new treatments for heart attacks and aortic aneurysms, that could one day be used in patients, we need to use some animals that also suffer a heart attack or aortic aneurysm. These are serious conditions and frequently lead to death in patients, so these animal protocols are severe in category. However, death usually occurs suddenly with only transient suffering. If the animals are suffering, they will be given suitable treatment and if this does not alleviate the suffering promptly, they will be killed humanely. All animals will be killed humanely at the end of the studies. The enormous burden and severity of heart attacks and aneurysms in patients warrants the use of severe category animal protocols in order to find new treatments.

A retrospective assessment of these predicted harms will be due by 28 July 2024

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.

My group is a world leader in using human stem cells generated from patients to develop cell culture based models of human disease that can replace the use of animal models in some circumstances. Together with collaborators, we have replaced the use of a mouse with a genetic abnormality that predisposed to heart disease (the 9p21 mouse) with a human stem cell model instead.

However, it is not possible to model many of the complexities of cardiovascular disease such as interactions of different cell types, immune response and blood flow in culture. Some aspects of disease including assessment of new treatments still require animal studies. Indeed it is usually not possible to take new treatments forward to patients without comprehensive animal studies.

A retrospective assessment of replacement will be due by 28 July 2024

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.

Using the human stem cell disease models that we are pioneering, many aspects of understanding disease mechanisms and testing new treatments can be carried out in cell culture so greatly reducing the number of animals required for final validation. As an example, we have developed a human stem cell model of Marfan syndrome - a genetic abnormality which is passed down in families and results in aortic aneurysms. Using just patient derived stem cells, we identified a new disease causing signal, and published the reults in a prestigious scientific journal (Nature Genetics) with no animal usage at all. Testing of new treatments and final validation of new mechanisms does however require animal models, although these are minimised by the extensive cell culture work already carried out.

Similarly, we are generating heart cells from human stem cells and making engineered heart tissues from these in culture. We can test many combinations of cells and materials in culture this way in order to optimise how we regenerate damaged hearts. This strategy of testing engineered heart tissues in culture will again reduce the number of animals finally used in the definitive tests of this approach.

In addition we also aim to use noninvasive imaging such as ultrasound (recently purchased for £300,000) that can be used repeatedly in the same animal with minimum discomfort, so needing fewer animals to obtain information from multiple time points.

We have recently developed a method to turn key genes regulating heart and blood vessel diseases on or off using a lentivirus intravenous injection to deliver the signal. This will reduce the number of genetically modified animals that will need to be bred together to switch genes targeted to blood vessels on or off.

A retrospective assessment of reduction will be due by by 28 July 2024

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.

Animals are housed according to the best recommendations in an appropriate and enriched environment. We collaborate extensively with experts including those in the USA to obtain the benefit of their experience in refining the protocols; so we minimise the effects on the mice and rats and subsequently pain, distress and suffering.

We are pioneering new approaches to refine the surgery for heart repair such as a percutaneous needle based approach to delivering cells and even patches to the heart without requiring an open heart operation.

A retrospective assessment of refinement will be due by by 28 July 2024

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?