



Home Office

## NON-TECHNICAL SUMMARY

# Mechanisms of diabetes-associated heart disease

### Project duration

5 years 0 months

### Project purpose

- (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

Diabetes, Heart diseases, Heart attack, gene function

## 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?

The aim of this project is to determine the fundamental role of genes involved in diabetes-associated heart disease, in particular the effects of diabetes on the development of heart dysfunction. The objective is to develop the treatment strategies of heart dysfunction, particular in diabetes.

**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?**

Diabetes affects 10% population worldwide. Approximately 57% diabetic people will develop some degree of damage to heart function. Diabetes not only affects structures and function of heart muscles, but also causes poorer prognosis after heart attack. This project will benefit diabetic patients suffering from heart disease by identifying new treatments to improve heart function.

**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?**

The designed work will be conducted in mice for the duration of 5 years, which includes five thousand animals. Genetically modified mice will be used to study the role of genes in the heart.

## 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?**

Mouse models will be used to study the effects of both types of diabetes on heart disease. With both models, animals will have raised blood sugar levels, eat and drink more, and urinate more frequently than control mice. Animals are regularly checked, and cages are changed daily. We typically use streptozotocin to develop Type 1 diabetes on mice, in which loss of body weight may occur. Type 2 diabetes will be induced by high calorie food, obesity or skin irritation may occur. At any stage, if the mice display any distress or lose a lot weight, they will be killed humanely.

When checking blood sugar in models of diabetes, we may remove food from the cage for 6-18 hours, which may irritate the animals though water will be always provided. A small amount of blood will be collected under local anaesthesia to reduce stress in the animals.

Administration of pharmacological agents by injection or oral route (gavage) may cause transient stress. Where appropriate pain relief medication or local anaesthesia will be provided. The animals will be carefully monitored to ensure effectiveness.

Post-heart attack injury will be induced under terminal anaesthesia by ligation and subsequent untying one of the major blood vessels of the heart (coronary artery). These mice will not recover after surgery.

To assess cardiovascular function, mice will undergo a series of tests, including ECG for heart rate and rhythm, blood pressure which are not performed under sedation and cause little stress to the animals. Cardiac ultrasound will also be performed under general anaesthesia. These tests may be repeatedly performed, in which the animals will recover from general anaesthesia and be reused. The welfare of the animals in these longitudinal studies will be carefully monitored.

## Replacement

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

The anatomy and physiopathology of the heart in mouse is similar to the human heart. Diabetes is a whole-body disease, affecting hormone, immune and cardiovascular systems, which cannot be effectively tested in non-animal systems. Hence, there are currently no alternatives to the use of mice.

Cultured heart cells or isolated heart complement our understanding of gene function and treatment dose or efficacy. If any relevant non-animal alternatives become available during the course of the work, we will incorporate these in our projects.

## Reduction

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

We will use statistical Power Calculations based on our previous experiments and experience, which allows us to minimise the number of animals.

We will use efficient and optimised breeding protocols to minimise animal number. In addition, the use of control animals can be reduced, because the variation between these mice is lower. Where possible control data from previous experiments may be used to minimise controls.

## 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.**

Gene changed mice are well-established models for studying the cause of heart diseases in human. Although gene changes may result in unexpected suffering, these occurrences are rare, and the mice will be monitored at all stages.

To minimise the harm to the mice, we will continue to use/improve these refined approaches and techniques, causing the least pain and distress whilst being able to meet our objectives.

Blood collection and administration of pharmacological agents by injection or oral route (gavage) will be performed with pain relief medication or local anaesthesia. Mice will be carefully monitored. We are familiar with the methods, and no adverse impact on animal welfare is expected.

Induction of post-infarction injury by ligation and subsequent untying of coronary artery will be carried out under general anaesthetic to ensure that the mice do not feel pain. The mice will not recover.

Echocardiogram will be performed under general anaesthesia, while ECG and blood pressure check are performed on conscious mice, which is free of stress. In the majority of cases, heart function tests will be performed under terminal anaesthetic from which mice do not recover.

At any stage, any mice showing signs of distress will be evaluated in consultation with the veterinary surgeon and killed humanely if the distress cannot be averted.