G. Non-Technical Summary (NTS)

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

Inherited cardiac conditions (ICC) are cardiac diseases caused by abnormalities in the DNA (mutations) and can be transmitted from parents to children. In this project we will investigate two different types of ICCs:

1. Inherited arrhythmia syndrome (channelopathies)

2. Genetic cardiomyopathies.

These conditions usually affect adolescents and young adults.

Channelopathies are caused by abnormalities in the electrical properties of the heart that lead to irregular heart rhythms (arrhythmias) which can sometimes lead to sudden death. Novel treatments have been proposed to prevent arrhythmias. However these have not been widely tested. Channelopathies vary in their severity: in some family members there is no evidence of any arrhythmias but in others there are severe arrhythmias which can cause sudden death. The factors that determine this variability are not known, though some studies suggest that diet and pollution are important.

Genetic cardiomyopathies are conditions characterized by alteration in the structure and function of the heart. We intend studying 2 types of cardiomyopathies which cause heart failure and serious symptoms including death. We can identify family members who carry the genetic defects very early before they develop the cardiomyopathy. However currently we do not have any treatments to prevent or reverse them. Again, there is variability in the severity of the condition within a family. Diet and pollution have also been suggested as potential factors that influence the severity of the condition.

This project has 3 main objectives

1) To develop new treatments for arrhythmias and the 2 types of cardiomyopathies

2) To better understand whether dietary modifications affect the severity of these conditions

3) To better understand whether pollution modify the severity of these conditions

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)?

This project could identify new treatment strategies for these patients that could significantly improve their symptoms and prolong their lives. Identifying environmental pollutants which influence the severity of these conditions would be a valuable asset to the public health community

Private & confidential: *Please be aware that the contents of this form may be made public resulting from the "Freedom of information Act". Personal details will not be released.*

What types and approximate numbers of animals do you expect to use and over what period of time?

Mice 10700 over 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?

We will inject certain drugs to induce irregular heart rhythms (arrhythmias). The onset of arrhythmias can cause difficulty in breathing in the animals. We will perform the study under anaesthesia to reduce animal distress. Some of the genetic alterations we study can cause thickening of the heart muscle or enlargement of the pumping chambers of the heart. If these changes become severe they can cause heart failure. The typical signs of heart failure are decreased food intake, weight loss and difficulty in breathing. We will monitor the heart structure and function with heart scans. To prevent the onset of heart failure the in vivo studies will be terminated when the changes in heart structure are moderate. We will give drugs or substances that can cause adverse effects such as decreased food in intake and weight loss. The animals will be carefully monitored for these signs. The animals will have operations that can cause infection or bleeding which will be prevented by appropriate care of the animals. The severity level of this study is going to be moderate All animals will be humanely killed at the end of the in vivo studies.

Application of the 3Rs

Replacement

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

Replacement

Arrhythmias and enlargement or thickening of heart muscle cannot be studied in single cells or tissues slices. They must be studied in vivo using animal models.

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

We have carefully designed the study to reduce animal use . We have carefully calculated the minimum number of animals needed for each experiment. Animals used for the in vivo studies will also be used for the in vitro studies after they have been sacrificed. We will also use tissue from each animal in more than one in vitro experiment, so that the numbers needed will be drastically reduced.

Refinement

Explain the choice of animals 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.

Refinement

Mouse models reliably reproduce the clinical signs of these inherited cardiac conditions. Therefore, mice are the lowest sentient animal suitable for this work.

We will terminate the study well before the development of advanced cardiomyopathy, so it is very unlikely that the animals will develop any symptoms of heart failure which can happen in advanced cardiomyopathy.

We will run a pilot to determine whether we can minimize the stress to the animals when we induce arrhythmias under general anaesthesia.

Phenantrene, a common air pollutant, has been associated with weight loss at very high doses which are well above the range proposed in the study. It is therefore unlikely that the animals will experience weight loss. However we will monitor animal weight closely to ensure this does not happen.