



Home Office

## NON-TECHNICAL SUMMARY

# Hypoxia and its role in the transcriptional modulation of physiological response

### 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.
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants.

### Key words

Oxygen, hypoxia, heart attack, stroke

## 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 aims are to better understand how low oxygen levels in tissues can impact how those tissues survive and function. We aim to understand how the interruption of blood flow, which occurs in both heart attack and stroke, can lead to oxygen deprivation, and how that in turn can cause changes to tissues; those changes can allow adaptation to reduced blood flow and oxygen supply, but sometimes lead to tissue damage, something we would like to understand.

**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?**

A significant killer of people in the UK is heart disease and stroke. Both of these occur because blood flow is interrupted to the heart and brain, respectively. When blood flow is halted, oxygen does not get to these tissues, and as a result tissue damage and even death occur. A better understanding of how tissues respond to loss of oxygen will help treat these diseases more effectively, and help us better prevent the damage that loss of oxygen gives rise to.

## **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?**

We use mice, and anticipate using 20,000 over the five year course of these experiments. Our experiments involve very complex genetic modeling, with many genes altered simultaneously in the same animal; all of the genes we work on are involved in the complex responses of tissues to oxygen deprivation. To obtain these extremely complex mice, equally complex breeding schemes are necessary that give rise to significant numbers of mice. We use state of the art genetic monitoring to minimize the numbers created and used, however, and keep them to the absolute smallest number required to gain scientifically reliable results.

## **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 many of these experiments, the adverse effects are mild, in that animals do not suffer undue stress by being subjected to the levels of oxygen employed by us experimentally. They will experience some increase in breathing rates and slightly lower levels of activity, much as is experienced by mountain climbers and other people at high altitudes. Some animals will have surgically implanted units used to monitor parameters such as blood pressure and heart rate. When this is done, all procedures will be

carried out with aseptic surgical techniques and appropriate levels of anesthesia, and pain relieving drugs will be administered during recovery from surgery. On occasion, humane techniques will be used to obtain blood and urine samples, and drugs will be administered in some cases as well. Animals will be killed humanely at the end of experiments.

## Replacement

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

The response to low oxygen is very complex, and to better understand how it impacts tissues during cardiovascular and other diseases, it needs to be studied in whole animals rather than in tissue culture/cell systems alone. . This is particularly true when one wishes to understand, as we do, how the interaction of multiple tissues at once gives rise to coordinated responses by the body to low oxygen levels]. Additionally, we use cell co-culture systems wherever possible to model simple cell-cell interactions. Such co-culture systems are an important mechanism for replacement of living animals. We will continue to explore such systems for co-culture of multiple cell types to allow us to replace use of animal models wherever possible.

## Reduction

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

We always use the minimal number of animals necessary based on statistical calculations and then using only those animals needed to obtain a reliable result. We do pilot experiments with small numbers to gain an initial understanding of the degree of change our experiments cause in the response to low oxygen, and only after understanding that do we carry out a larger experiment designed to use the smallest number of animals necessary to get a scientifically and statistically reliable understanding.

## 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.**

We use pain relievers and other agents to minimize effects of procedures on animals, whilst in pursuit of our experimental objectives. We use mice, as they are a species that has high relevance to humans in regards to physiological response to low oxygen, and their genes can be readily modified to enable us to investigate specific pathways/genes of interest in a way that cannot, for ethical reasons, be completed in humans. Our animal models are state of the art and engineered to directly address pressing questions related to cardiovascular health.