



Home Office

## NON-TECHNICAL SUMMARY

# Hypoxia and Cancer: Molecular Mechanisms and Therapeutic Strategies

### 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

Hypoxia, cancer, metastasis, immunotherapy

## 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 understanding of the relationship of oxygen to cancer is key to a better understanding of cancer progression. Work by many scientists has shown that cancers are typically lacking in sufficient oxygen (a condition known as hypoxia), and that this lack appears to drive cancer dissemination to distant sites in the body, or secondary cancer (metastasis). Metastatic disease is the leading cause of death for cancer patients. We have shown that the mechanisms and molecular players activated in response to hypoxia during cancer growth and dissemination play an essential role in allowing or preventing the cancer progression, and in fact activate different cell types in different ways. During the tenure of this license, we aim to manipulate the hypoxia pathway in a way that elucidates what is necessary for tumour growth and colonization of distant organs. We will also determine how hypoxia affects the ability to treat those cancers and prevent secondary disease, namely by exploring the role of both the immune cells, which can be activated to remove and kill cancer cells, and the blood vessels, which allow the transport of tumour cells from the site of origin to other organs. By increasing our understanding of how the response to low oxygen increases cancer progression, and which cells are responsible for that phenomenon, we expect to find tools circumvent or avoid those responses to both treat cancer and prevent metastasis.

**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?**

Most current therapies are very toxic, and cause a great deal of damage to non-cancerous tissues and organs, often also resulting in resistance and refractory disease. Also, there are no therapies to specifically target secondary cancer. Understanding these pathways will help us predict cancer progression as well as specifically target the treatment type, the treatment duration and time frame, to specific patients and specific cancer types, potentially avoiding or reducing the use of cytotoxic drugs in some cases. Targeted therapies that are specifically focused on individuals and their cancer type would greatly minimize the often devastating side-effects of treatment and increase efficacy; Our new findings in immune cell activation have great potential to transform this therapeutic avenue by making it applicable to cancer types that so far have been considered unresponsive to this approach.

## **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?**

Mice will be used exclusively. We will use approximately 20,000 mice over the five year period of this protocol.

## **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?**

Animals will develop tumours, but in most models these will not cause any pain or discomfort within the time frame of the experiment. We will also use early humane endpoints as well as pain relief in order to prevent any unnecessary animal suffering. All mice will be humanely killed at the end of these experiments and tissues taken for further analysis.

## Replacement

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

Cancer is a very complex disease, and progression of this disease cannot be fully modelled in any other system than an animal. Unfortunately, growth of cells in dishes cannot recapitulate the complex interactions necessary for the development and maintenance of cancer. We do use cell cultures to test simple hypotheses, and when feasible, to better understand how molecules that affect cancer growth interact with each other.

## Reduction

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

Pilot experiments are always performed using a small number of animals to refine the experimental procedure and design, so as to minimise overall animal numbers used.

Any questions that can be answered using isolated cells, or combinations of cell types, will be preferentially used so as to avoid unnecessary use of animals.

We will only produce mice in response to very specific and required experimental demands.

## 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.**

Mice are ideal models for the studies we propose within this license for several reasons, including their high physiological and metabolic resemblance to humans, which makes cancer origin and progression in these animals similar to that seen in humans, and the research results likely applicable for further applications in human disease.

We use the earliest endpoint possible to stop experiments, that still allows scientific value. We use routine monitoring of mice that may develop tumours to ensure that animals only develop cancers to

pre-determined stopping points. We randomise and blindly assess results so as to avoid biases and confounding factors, and determine the endpoint of experimental animals using their welfare as the primary criteria.

Animals will always receive pain relief and anaesthetics if and as needed.