NON-TECHNICAL SUMMARY

Genetic determinants of renal cancer progression

Project duration
5 years 0 months

Project purpose
None selected

Key words
Renal cancer, genetics, carcinogenesis, metastasis

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 is the aim of this project?

Renal cell carcinoma is the most common type of kidney cancer affecting 8,000 people and causing 4,000 cancer related deaths each year in the UK. Despite recent advances in our understanding of the underlying molecular biology and the development of novel therapeutic agents it remains an incurable
disease once it has spread, i.e. formed metastases, outside the kidney. The vast majority of metastatic cancers are refractory to treatment and are therefore incurable. Thus, there is a pressing clinical need for further research on the molecular basis of renal cancer.

The goal of this project is to understand genetic factors that are required for initiation, maintenance and metastasis of renal cancer. Such knowledge is essential for the development of rational new treatments for this disease.

Amendment (July & September 2020)

To assist in achieving the above goals, amendments have been added to improve the techniques we use to establish and monitor these mouse models of renal cell carcinoma. In addition, we have added intravenous (directly through the bloodstream) as a route of administration for substances, as it allows the substance given to reach the target organ (kidney) in a quicker and more physiological (normal) way like how we observe in humans.

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?

The expected benefit from this work is a better understanding of which genes are important for renal cancer growth, and how at the molecular level these genes promote renal cancer. Thus, the potential secondary benefits of this work will go beyond basic cancer research, and might prove valuable to clinicians by possibly leading to the identification of (i) new drug targets for kidney cancer and other cancer types (ii) new biological markers that can be used to predict how renal cancers behave in patients.

Amendment (July & September 2020)

Improving these techniques for establishing mouse models of human renal cell carcinoma will improve the ability to establish a robust experimental platform that is more reflective of the human disease. This in turn increases and improves the translatability of findings from this animal research into the clinical setting where there is an urgent need to improve the management of this disease.

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?

1700 mice 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?

Tumour induction, which means injection of cancer cells under the skin, into the vein, into the heart or into the kidney, will in most cases have no significant impact on animals' general well-being. Short-term mild discomfort may be possible directly at the injection site but animals are expected to recover quickly. In some cases, such as where surgical procedures are used, the mice will receive pain-relieving drugs in order to reduce the injection-related adverse effects. In very rare occasions tumour induction may result in sudden death without preceding signs.

After tumour induction, animals will be observed closely for any evidence of tumour growth by physical examination, inspection of the injection site and whole animal imaging. Discomfort resulting in moderate clinical signs such as hunched posture and inactivity or respiratory distress will result in individual animals being killed and on occasion the termination of the experiment.

For other procedures such as drug treatment most animals will show no more than mild clinical signs. In drug experiments control animals will receive vehicle. Some may show moderate signs such as hunched posture, loss of body weight, lack of grooming, which will require termination of the experiments by killing the animals.

At the end of experiments, all animals will be humanely killed.

Replacement

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

Understanding the genetic and molecular mechanisms that support the development of cancer requires investigation in model systems that replicate as close as possible the human disease (cell and tissue of origin, surrounding environment). These parameters cannot be replicated in tissue culture systems in the lab. The laboratory mouse represents the best available model system for cancer owing to various factors including its extensive biological similarities to humans, and an entirely sequenced genome. We will therefore utilise animal models in order to validate findings that we initially make using tissue culture experiments in the lab.

Reduction

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

We will aim to minimise the numbers of animals used by:
(1) Using tissue culture experiments to identify genes that are likely to be important for cancer growth before starting animal experiments.

(2) Careful planning and statistical analysis will help us use the smallest number of animals that will ensure robust results.

(3) Once experimental end points are reached, cancer tissue from affected animals will be harvested to facilitate continuing, complementary work in the laboratory.

(4) Pilot studies on small groups of animals will reduce the number of animals used.

(5) Imaging techniques such as bioluminescence, i.e. detection of light produced by a reporter gene that is expressed by the cancer cells, will allow further reduction in animal usage.

(6) Whenever possible, the experiments will be randomised and the investigator will be blinded to the experimental groups.

**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.*

Mouse models have been chosen as they represent the least sentient species able to generate meaningful data, i.e. that is likely to be directly applicable to the human disease.

Animal suffering is minimised by the use of appropriate pain-relieving drugs. Where clinical signs are seen animals will be killed as soon as possible and before they are likely to develop signs of pain or distress that would exceed a moderate severity limit.