G. NON TECHNICAL SUMMARY (NTS)

Project title: Genetic Dependencies of Renal Cell Carcinoma
Duration of project - years: 5
Duration of project - months: 0

Purpose of the project (as in ASPA Section 5C(3)):
(a) basic research: YES
(b) translational or applied research with one of the following aims:
   (i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their
       effects, in man, animals or plants: NO
   (ii) assessment, detection, regulation or modification of physiological conditions in man, animals or
       plants: NO
   (iii) improvement of the welfare of animals or of the production conditions for animals reared for
       agricultural purposes: NO

(c) development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs
    and feedstuffs or any other substances or products, with one of the aims mentioned in paragraph (b):
    NO
(d) protection of the natural environment in the interests of the health or welfare of man or animals:
    NO
(e) research aimed at preserving the species of animal subjected to regulated procedures as part of
    the programme of work: NO
(f) higher education or training for the acquisition, maintenance or improvement of vocational skills:
    NO
(g) forensic inquiries: NO

Keywords:
Renal cancer, genetics, carcinogenesis

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):
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 spread outside the kidney. The study of renal cancer pathogenesis and the development
of more effective treatments have been hampered by the limited availability of appropriate genetically
defined animal models of the disease. The development of reproducible and accurate renal cancer
mouse models will allow in depth investigations of the underlying tumour biology and the discovery of
new methodologies for the detection, management and treatment of human cancer.

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)?:
The primary potential benefit relates to new knowledge about the initiation and progression of renal
cancer. We will aim to publish the findings in academic journals and this information is likely to be of
interest to pre-clinical scientists interested in tumour biology. The secondary potential benefit relates to
the value of the results to clinicians and to the possibility that new therapeutic targets may be identified,
for which new pharmaceutical products could be developed. Thirdly, any developed mouse models of
renal cancer will be made freely available to academic collaborators and will represent an invaluable
resource for the early evaluation of novel methods for the detection and therapy of renal cancer.

What types and approximate numbers of animals do you expect to use and over what period of time?:
3750 mice 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?:
Mice used for breeding and maintenance of colonies are not expected to develop any adverse effects. In the experimental protocol, the mice will receive gene-inducing agents either via food, water, or injections. Injections will be used if the transgene-inducing agent needs to be administered in few occasions only, for continuous administration the agent will be administered via food or water. After gene induction, the mice will be followed by general health checks as well as imaging techniques that allow the detection of internal tumours in living mice. During imaging the mice will be anaesthetized. The imaging procedures are not expected to cause harm. Some of the mice may also receive potential anti-cancer or cell labelling agents via food, water or injections. Some of the mice are expected to develop renal tumours and some may as a consequence experience abdominal distention, haematuria, weight loss and reduced activity. We expect these to occur in less than 15% of experimental mice. Following completion of experimental procedures mice will be killed, after which tissues are collected for molecular analysis.

Application of the 3Rs

Replacement:

The elucidation of the genetic events and mechanisms critical for the development of cancer requires investigation within model systems that replicate as close as possible the human disease (cell and tissue of origin, surrounding environment, immune system etc.). These parameters cannot be replicated in culture systems. The laboratory mouse represents one of the best available model systems for cancer owing to various factors including its extensive biological similarities to humans, and an entirely sequenced genome. Furthermore, genetic modification of the mouse genome can be easily and efficiently achieved.

An important aim of this project is to generate improved mutant mouse lines that are prone to the development of renal cancer. Such mouse models will be useful to determine the significance of various genes in the development of the human disease. In addition, a robust and reliable mouse model of renal cancer will be a useful system for the pre-clinical evaluation of diagnostic and therapeutic approaches. This model will be a valuable addition to the currently used systems (cell cultures, transplantation mouse models) that have proved of limited clinical prognostic value.

Reduction:

We will aim to minimise the numbers of animals used by:

(1) Investigating candidate genes and therapies in culture systems prior to generating mouse models
(2) Reduce the amount of breeding required to produce experimental and control animals

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at https://www.gov.uk/government/publications/government-security-classifications. Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location. All government information may be subject to an FOI request and subsequent assessment.
(3) Determining the approximate lifespan of the various renal cancer models in small pilot studies and collaborating with biostatisticians at our institute to determine the minimum number of mice that are required for any studies in order to reach conclusive results with suitable certainty

(4) Creating a tissue repository from generated mice to use in future experiments and share with other researchers

(5) Ensuring that none of our investigations duplicate work already performed

Refinement:

Mice are a well-studied experimental species whose genome can be easily and efficiently modified allowing the investigation of complex genetic diseases like cancer. The models used in our studies will allow us to control and direct genetic changes to the stage of development and tissue relevant to the purpose of our studies (i.e. the kidneys of adult animals) thereby limiting the effects of modified genes to other organs/systems. We will only use well established reagents and protocols and where novel methods need to be employed, potential harms will first be carefully characterised in small pilot studies.

We will aim to detect the development of kidney lesions as early as possible and therefore limit their effects on the health of the animals by performing regular health checks and imaging.

The staff of our animal facility has extensive experience in animal husbandry, welfare and disease and we will take advantage of their expertise to pick up signs of suffering early so that it can be minimised/alleviated.