Home Office

NON-TECHNICAL SUMMARY

p53 pathways in cancer and metabolic diseases

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

cancer, metabolic diseases, GA mice, therapy

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?

Cancer, a major health issue worldwide, is caused by a series of changes in genes (genetic mutations). Understanding how these mutations change the normal cell to a cancer cell, and how such changes alter the way in which cancer cells interact with the rest of the body, is vital if we are to prevent and treat

cancer. Only in the context of the complete living animal can we fully understand how cancers develop, invade and spread to other organs (metastasise). Using genetically altered mouse models with the same genetic mutations as in the human disease (‘patient-like’ animal models) we can investigate the biological consequences of these mutations in cancer progression, and identity how cancer cells co-opt normal cells to drive invasion and metastasis. These models can also be used to understand how preventable factors, such as obesity, promote cancer development. The genetic changes that occur in cancer can be very variable and complex, but a few alterations are consistently found in many types of cancer and appear to be fundamentally critical for tumour development. One such alteration is mutation within the p53 gene, which changes the function of the p53 protein. Alterations in p53 lead to many changes that contribute to cancer development. We are specifically interested in how p53 controls metabolic pathways within the cancer cell and how p53 affects the interaction of the cancer cell with surrounding cells, such as fat cells and immune cells. Defining metabolic functions and adaptation of tumour cells will enable us to design new cancer drugs, and understanding the effect on the immune response may help us identify patients who will respond to the new generation of immunomodulatory cancer therapies. We are also looking at how p53 works in other responses such as aging, tissue regeneration or metabolic disease. This information will help us identify less toxic cancer therapies and may allow us to repurpose drugs that are presently used for the treatment of metabolic diseases such as diabetes for cancer therapy.

These questions can be addressed using well established protocols that will allow us to explore the interplay between p53, inflammation, immune responses and metabolism. Our ultimate aim is to develop new therapeutic strategies that can be taken forward into human applications

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?

This project will deepen our understanding of the underlying causes of cancer and metabolic diseases in general and of specific types of cancer which currently have a poor prognosis such as pancreatic and liver cancer. Knowledge of the genetic causes will dramatically improve our ability to diagnose, treat and prevent cancer, which affects almost half of the human population. We will also use mouse models to identify and test new therapies which will benefit cancer patients.

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?

This project uses mice (including genetically engineered models). We expect to use up to 7,000 mice per year over 5 years. It should be noted that 70% of these will not undergo scientific procedures, but will be used solely for breeding and maintenance of colonies.

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 be bred to achieve test subjects which may be predisposed to cancer and/ or obesity/diabetes. Approximately 70% of the mice will not show any adverse effects relating to their breeding and not undergo any procedures except for ear notching for identification and genetic testing. These will be humanely killed when they are no longer required for breeding. A proportion of animals (no more than 25%) will develop diseases because of their genetic makeup or because tumour cells have been implanted and allowed to grow. This may require administration of an agent to switch on/off particular genes which only causes momentary discomfort but reduces off-target effects in other tissues. Animals will be monitored closely by highly trained staff for well-established clinical signs such as weight loss, swelling of the abdomen, and development of visible or palpable tumours. Some of these animals (15-20%) will be given anti-cancer treatments, changes in their diet or cancer causing agents (for example chemicals/irradiation). All animals on treatment will be closely monitored and may be blood sampled to follow changes in biomarkers which should cause only mild handling stress and momentary discomfort, or may be imaged. Any animal that displays signs of illness such as immobility or ruffling of the coat will be humanely killed. At the end of the study all animals will be humanely killed and tissues collected at post-mortem to gather as much information from the study as possible.

Replacement

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

Although many aspects of cancer research can be conducted using cells, it is impossible to fully model the complexities of a tumour, which is an interaction of many different cell types (tumour cells, immune cells, blood vessels). Furthermore, the ability to monitor how cancer cells invade and spread to other organs requires an animal model. Finally we know that cancer cells respond differently in the lab to anti-cancer therapies as they do in the context of the living organism and so testing the efficiency of such therapies requires a complete animal system. For metabolic diseases, changes of whole body metabolism or organ functions due to different diets such as high sugar high fat diet cannot be recapitulated using cell system.

Reduction

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

We perform preliminary experiments using only a few animals, before scaling up to the appropriate numbers for a full study. Numbers are calculated based on our experience using the same models, published literature and advice of our in-house statistical experts. We also share animals between experimental groups where possible e.g. when we need normal animals for controls, we can often obtain these from our breeding colonies where they would normally not be needed in a study. We

constantly optimise our breeding strategies to minimise the number of animals needed to achieve the desired genotypes for our studies and we use tumour transplant models where appropriate, which do not require breeding of genetically altered animals and thus use fewer animals in total per study.

To reduce numbers of experiments we also perform studies using cell lines or 3D models so that only our strongest hypotheses are tested in the mouse.

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 mouse models with the same genetic changes that are known to cause human cancer – so accurately replicating the human disease. These genetic changes are specifically altered in the tissue of interest so that unrelated effects in other tissues do not occur. All animals are monitored regularly for signs of normal behaviour and are humanely killed if they exhibit moderate adverse symptoms. All staff are expertly trained in these clinical signs. Regular monitoring of mouse welfare allows us to complete studies at the earliest endpoint in which we observe a significant result to prevent unnecessary suffering resulting from high tumour burden.

We always refer to previous studies for adverse effects of anti-cancer or anti-diabetic therapies and when a group is given a treatment for the first time, we initiate the study with a small number of animals (n=3-6) which is closely monitored before extending to a larger number.

Animals are housed in a dedicated facility proactive with environmental enrichment and receive anaesthesia and analgesia as appropriate.