Home Office

NON-TECHNICAL SUMMARY

Mechanisms by which lung and pancreatic cancers evade the immune system

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.

Key words

lung, cancer, therapy, immune system

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?

Mutations in a family of cancer genes (RAS) cause about 20% of all human cancers and lead to 1.4 million deaths per year worldwide. So far attempts at blocking the function of RAS genes have been unsuccessful. There is therefore a need to develop new treatments for cancer patients where this pathway is important, in particular in major killers such as lung cancer, colon cancer and pancreatic cancer. Work carried out in this laboratory in the past has aimed to identify novel ways of killing cancer cells with mutations in RAS using both cell culture work and mouse cancer models. We have found combinations of drugs that are able to cause major regressions of cancers in these mice, several of which are being taken forward into clinical testing in human patients.

However, while this is very encouraging, we also know that tumours in these animals are not completely eliminated and will regrow after therapy is discontinued. We wish to continue these studies to address how we can turn short-term tumour regressions into long-term cures. In order to do this, we wish to investigate the interaction of the immune system with tumour cells as they die in response to our new drug combination therapies. We plan to explore what parts of the immune system recognise the dying tumour cells and what is preventing the immune system from then fully rejecting the tumour. We will test whether precision targeting of some of the brakes that the tumours apply to the immune system might be able to work together with the drug combinations we have already tested to cause complete cancer cure.

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 potential benefits of this work lie both in advancing basic scientific understanding of cancer as a disease and in providing insights into new clinical strategies for the therapy of common cancers. In our work on therapeutic drug combinations and promoting the ability of the immune system to work together with these to eliminate tumours, we hope to provide clear rationales for the design of new clinical trials in cancer patients that optimally combine the very latest targeted drug combinations with immunomodulatory drugs. These should have implications in terms of improvement in therapy for large numbers of cancer patients, particularly the 450,000 patients diagnosed each year worldwide with RAS mutant lung tumours and 300,000 patients diagnosed each year with RAS mutant pancreatic cancer.

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?

The project will use exclusively mice and will run over five years. During that period, we expect to use up to 76,750 animals.

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?

This project focuses on the study of lung and pancreatic cancer in mice that are genetically prone to developing these diseases. The major adverse effects that we expect to see are therefore those associated with the development of these cancers. If the disease is allowed to progress unchecked then the mice would ultimately die from its effects, which could involve unpredictable levels of suffering. We will therefore take great care to closely monitor the progress of the disease and will humanely kill the mice before the cancer progresses to a point where it can cause suffering. As these cancers occur in internal organs, this requires the use of scanning technology similar to what would be used for cancer patients in hospital – computerised tomography (CT) for lung cancer and ultrasound for pancreatic cancer. Experiments will be designed so that mice would be treated over a period when the cancers would not be expected to have progressed to an extent that would cause suffering to the animal. Another possible source of adverse effects is the use of drugs to treat the cancers, including experimental agents not yet used in a clinical setting; as with the treatment of cancer in human patients, these drugs can sometimes have serious side effects. To avoid potential suffering from the side effects of drug treatments, mice will be monitored very closely when on treatment. If they show any signs of suffering, such as significant weight loss or changes in behaviour or condition, they will be humanely killed. Rare instances may occur where rapid progression of the cancer could result in death from the disease, or its treatment, before any signs of suffering were detectable, despite stringent monitoring. It is expected that the rate at which this would occur would be no more than 5% of the animals bearing tumours in internal organs in experimental drug treatment studies, and considerably lower for other animals. Animals will be humanely killed at the end of the defined experimental period or at the first detectable sign of suffering caused by the cancer or its treatment. Other possible sources of adverse effects could involve the use of anaesthetics and restraints, for example during scanning procedures. These procedures are only carried out by very experienced practitioners and problems are extremely rare; again, animals are monitored very closely and will be humanely killed if any signs of suffering are seen.

Replacement

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

We have extensively used cultured cancer cells in the run up to this project. We have also used bioinformatic analysis of publicly available data from cancer genome sequencing studies. However, various aspects of the cancer disease process can only be addressed in living animals. The development and function of the immune system, which is a focus of most of our work, involves many different cell types that cannot be mimicked in vitro. The interaction of the tumour with the immune system and how it responds to immunotherapy can only be accurately studied in live animals.

Reduction

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

We have used in vitro cell culture systems to define a limited set of hypotheses that merit testing in animal models. Mouse breeding experiments have been planned in detail in consultation with experts in statistics and animal breeding. We will ensure that the minimum numbers of animals are used to obtain statistically meaningful results. In practice, for therapeutic studies this involves performing pilot experiments conducted with cohorts of five mice each; these preliminary data are then used to plan appropriately powered experiments using mouse numbers that should give statistically significant results. Mouse colonies will be actively managed to ensure that the basic principles of mouse breeding will be adhered to and only the minimum number of animals required for the experiment are generated. In addition, the use of in vivo imaging methodologies such as micro CT scanning greatly reduces the number of animals needed compared with end point assays as each mouse can be followed over time and inter-mouse variability is internally controlled for.

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.

The mouse closely resembles humans in its susceptibility to cancer. Mice can be genetically altered and have been extensively used for the topics of our investigation. We aim to develop mouse cancer models that accurately mimic the human disease, with relevance to some 20% of human cancers with mutations in RAS oncogenes. Only by allowing tumours to develop in these mice can we address the potential of targeting the molecular interactions that we are studying for treating human disease. The severity of the procedure will be limited by ensuring that animals are killed as soon as overt signs of the disease can be seen, and that mice are rigorously monitored for signs of suffering or distress at all times. These studies address the response of tumours to experimental therapies, but have been designed to focus on mice with early stage disease, in which setting the impact of the tumour on the overall health of the animal should be small. Drug treatment will involve only the use of agents that have already be tested on mice, so will not involve chemicals where unexpected toxicities are likely to occur.