



Home Office

NON-TECHNICAL SUMMARY

Developing therapeutic drugs for cancer

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.
- (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 purpose (b)

Key words

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?

The aim of this project is to develop new and improved medicines for the treatment of cancer.

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?

Our project plan involves all aspects of cancer drug discovery and development including developing new cancer models (experimental systems that mimic aspects of the human disease), testing how effective potential new drugs are and determining the best way to combine new drugs with existing treatments. We have a track record of successfully developing new cancer therapies that go on to receive approval from regulatory agencies to be prescribed to cancer patients. Under this licence we expect to continue to advance new cancer therapies to the clinic.

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?

We expect to use up to 41,500 mice and 700 rats over the course of 5 years. Typically, this may support assessment of up to 30 new drugs and targets for cancer therapy.

These numbers were calculated based on our use over the last few years, and an expectation that we will continue to perform similar studies at a similar pace.

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 are kept in high-quality facilities, free from pathogens and with access to food, water, and environmental enrichments. In all the facilities used, the animal care staff are highly trained in mouse welfare and will ensure the animal suffering is minimised. Animals are group housed except in exceptional circumstances such as when aggressive behaviour risks animal welfare or when cage mates have been removed for experimental reasons. In nearly all cases, mice will be between 6-12 weeks of age when they enter into studies, however we plan to use a small number of older mice up to 18 months of age in order to understand the effects of age on tumours and on our experimental therapies.

Most of the animals will be used for studies that measure the impact of experimental drugs on tumour growth rates. The vast majority of tumours will result from injection of tumour cells under the skin which then grow into a tumour at the site of injection. However, in some instances we will introduce tumours

into specific organs through specialised injection routes. For example, direct injection into breast tissue mimics breast cancer, while injection into the blood stream leads to tumour growth in the lungs. Producing tumour growth in other internal organs requires surgery, such as to implant tumours into the pancreas or the intestines. This involves making a small surgical incision into the abdomen plus injection of tumour cells directly into the organ followed by closure of the wound. Tumours that grow just under the skin are easy to observe and to measure their size using callipers. Tumours that grow internally are more difficult to observe therefore other methods are employed such as the use of non-invasive imaging techniques and/or clinical scoring systems to carefully monitor the well-being of each animal.

In some cases, it is not necessary to use mice bearing tumours. For example, tumours are often not needed to determine whether a drug is tolerated by the mice or to measure how much of a drug enters the bloodstream.

In addition, we sometimes can use animals that do not carry tumours when we wish to understand the impact of our drugs on specific aspects of the immune system. In these instances we are able to use experimental systems that allow us to ask very specific questions in the absence of a tumour.

In all of these studies, the likeliest sources of adverse effects are from the size and condition of the tumour, from surgical procedures, and from the drug treatment. All animals bearing tumours will be classified as experiencing moderate severity unless their tumours remain below 500mm³ and are also in good condition. We will humanely euthanize any animals that have developed advanced cancer to minimise unnecessary suffering. Animals undergoing surgical procedures will be also classified as moderate and pain relief or anaesthetics will be provided when necessary. On some studies, we will apply advanced non-invasive imaging techniques that allow us to track growth of tumour cells or to follow distribution of a drug throughout the body. To do so animals will be anaesthetised for the duration of the imaging session. Blood samples may also be collected during some studies to measure levels of drug substance or other indicators of drug effect over time. Blood samples are usually of a small volume and are taken from a vein in the tail or at the end of the study if larger volumes are needed. Drug substances are most commonly injected into the peritoneal cavity, intravenously, or directly into the tumour. Occasionally drugs may be administered orally. Treatment of animals with cancer therapies may also lead to unwanted effects similar to those experienced by patients. Most of these effects will be of short duration and mild but some animals may experience moderate effects. We expect that approximately 30% of animals will be classified as moderate, and the remaining 70% will be mild or lower severity. When animals are used that do not carry tumours, adverse effects similar to those mentioned above may result from treatment with cancer therapies.

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

Replacement

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

Although we do many experiments using cells, molecular biology, and computer modelling, it is still necessary to use some animals for research so that we can more accurately assess the interaction of cancer cells with other cells and organs within the body. Isolated cells and organs do not reproduce the

complex nature of in vivo biology. Animal models also allow us to understand cancer in the organ of origin or as it spreads throughout the body; this is important as when cancer spreads it is often fatal for the patient. An important aspect of our work is to understand how the immune system can be harnessed to attack tumours, and it is not possible to fully recreate these complex interactions outside of a living animal. In addition, regulatory agencies often require animal studies prior to approval for clinical trials.

Reduction

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

We acknowledge the importance of reducing the number of animals used and use statistical methods to ensure the correct number of mice are used to achieve our scientific objectives, which reduces the need to need for studies to be repeated in the future. Other measures such as random assignment of animals to treatment groups also increase the robustness of studies. We also always perform small pilot studies for new molecules or models to refine our systems before embarking on more complex experiments. We have implemented an innovative study design for tolerability studies to reduce animal numbers. During our previous projects we have characterised our models and maximised the benefit gained from each mouse by analysing tissues in the laboratory. This characterisation has been important for reducing animal use since it ensures we can select the most appropriate model for each experimental question, thereby reducing the overall number of models used.

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.

Rodents are the lowest species of mammal that allow us to adequately model the complexity of human cancer and immune system biology. The biology of rats and mice is well understood which enables rapid advancement of novel areas of research compared with other species. Many research tools also exist for rodents which enable experiments to be done in these animals that cannot be performed in other species such as zebrafish.

The most common tumour model that we use involves injection of tumour cells under the skin resulting in tumour growth at the site of injection. This is the simplest rodent tumour model available and the easiest to monitor therefore carries the least welfare risks. This model is preferred except in cases where we need to understand more complex questions such as the spread of cancer from one site to another, the influence that specific cell types and organs have on tumour growth, and the responses of tumours to our therapies in these varied settings.

We are committed to refining our procedures to minimize harm to the animals and have a track record of doing so. We ensure small-scale pilot or tolerability studies are carried out for new models or therapies. We carefully monitor tumour burden including the use of whole body imaging techniques

when possible, and we also use tumour-free mice in some cases when tumours are not essential. We have implemented innovative study designs to reduce animal numbers and enhanced health checks to minimize suffering. When unexpected severe events have occurred, we have investigated through post-mortem examinations.

We will continue to refine our work to minimise harm to the animals. We plan to investigate alternative methods for measuring tumours and for collecting tumour tissue which should reduce variability and hopefully reduce the numbers of mice used per study.