



Home Office

NON-TECHNICAL SUMMARY

Genetically engineered mouse models of 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.

Key words

Oncology, Tumour, Efficacy, mechanism, cancer

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?

Whilst current cancer treatments provide some survival benefits (50% survive cancer for 10 years or more in 2010-2011), they are often associated with significant side effects. Thus, there is a clear need for improved and better tolerated medicines that can be used either alone or in combination with existing or other new therapies. By combining 2 or more drugs it may be possible to see an enhanced benefit in treating cancer. Traditional cancer models do not accurately reflect all aspects of the tumour microenvironment observed in patients. Many new drugs are aiming to specifically target aspects of the tumour microenvironment that cannot be assessed in these traditional models. Genetically engineered mouse models have been shown to have a tumour microenvironment that more accurately reflects that seen in patients. The aim of this project is to develop new models and to profile potential new drugs and/or combination in genetically engineered mouse models to investigate efficacy, development of resistance and support the design of future clinical trials.

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?

In this project we will generate new mouse models. Using these models we will be able to better understand the efficacy of potential new drugs and drug combinations within a tumour that is clinically relevant. As such we can better define how to give compounds alone and in combination to have the optimal impact on tumour growth. This will significantly improve the cancer patient's quality of life and overall survival.

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?

Only mice will be used on this project. Up to 4850 mice will be used over 5 years under this PPL.

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?

Pilot studies will be performed to define the most optimal welfare endpoints for each different model type proposed to be used under this licence. The plan is to generate approximately 10 new models over the course of the licence. In these studies, we will monitor growth by relevant methods e.g calliper measure, palpation, imaging. Animal welfare, including weight loss and/or changes in clinical signs (e.g social isolation or ruffled fur) will be closely monitored in these studies. Animals will be closely monitored and humanely culled if adverse effects are observed. Animals are monitored by trained staff, with referral to the Named Animal Care and Welfare Officer, veterinary staff and Project Licence Holder

as necessary. The mice will be genetically engineered in a way that means that they will form tumours either spontaneously over time or in response to an inducing agent. Depending on the model this may be via a number of routes but is most likely to be via drinking water or orally. Inducing agents may be administered by a route under short term anaesthesia e.g directly into the lungs. In some rare instances there may be a need for mice to undergo surgery for the tumour induction. The least invasive route possible will be used and surgery will only be used when all other alternatives have been investigated. After tumour induction mice will be monitored for the growth of tumours. Animal welfare during tumour formation will be carefully monitored in pilot studies. The endpoints for each model will be defined and agreed with named animal care and welfare officer (NACWO) and veterinary staff prior to performing the larger scale studies. To get a better understanding of the models we will test known anti-cancer drugs to determine how well the tumours respond to therapies. These drugs will typically be given orally but may be via other routes including intravenous injection (IV), injection under the skin (subcutaneously) or in to the peritoneal cavity (intraperitoneal). These studies will help us to define how many mice would be needed to perform the optimal experiment to profile novel anti-cancer drugs in each new model. Once these experiments have been performed the licence will be updated to clearly define the welfare endpoints for each model. These tumour models will only be used where there is a scientific rationale for using these more complex model systems. Animals will be culled if the tumour results in significant pain or distress. In these studies clinical signs related to the compound may be seen and mild to moderate signs of toxicity are possible. Animals will be humanely killed if this persists. All animals will be regularly monitored for weight loss and general condition. Weight loss as a result of repeat anaesthesia may occur and this will be minimised by correct dosing and good maintenance of body temperature. Lung cancer is one of the most common forms of cancer worldwide and accounts for a significant proportion of cancer related death. In this licence we will use lung tumour models to investigate new potential drugs for the treatment of lung cancer. Where possible imaging will be used to ensure the mice being treated with anti-cancer drugs have developed tumours. In mice lung tumours have the potential to change the breathing pattern of a mouse and if this happens in a persistent manner, mice will be humanely killed. The protocols are classified as moderate severity. Animals will be humanely culled at the end of the study.

Replacement

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

Non-animal alternatives (in vitro systems) are used in the identification and selection of compounds and generally include measurements of the likely effect of the compound on the target cells. Complex systems for the culture of cells, including 3D culture systems or co-culture (combined culture of tumour cells, plus a different cell type of interest) can be used to increase understanding of a compound, particularly where traditional 2D culture systems are not informative. These systems are used to reduce the numbers of compounds that are required to be used in animals (i.e. in vivo) as only compounds that show the appropriate activity in cells are progressed further. To date there is no cell culture system that is able to predict the likely in vivo activity of compounds, given the high complexity of factors at play in a living organism, and in living tumours. For example, the accessibility of compounds to tumours, while avoiding toxicity to all other cells/organs can only be tested in vivo. Therefore the whole animal is needed for the studies proposed in this licence. We will continue to work with groups that develop assay systems that have the potential for replacement. Additionally we will continue to keep up with the

latest developments by attending conferences and monitoring websites, such as pubmed, for the latest advances.

Reduction

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

To maximise the scientific integrity of data generated and use the minimum number of animals, an in house statistician will review experimental design and analyses. The initial pilot studies will be used to drive these discussions with the statistician and perform power calculations. Based on historic data from these types of models we would expect to have group sizes of n=6-12.

There will be multiple projects within the portfolio that would gain additional insight to support progression by profiling compounds in the genetically engineered mouse models. We will maintain a list of required experiments for each project and ensure all preliminary work (e.g tolerability studies) is in place for these. This will reduce the risk of not having a use for experimental animals if projects are unexpectedly terminated.

The use of imaging on protocol 2 allows us to identify mice with tumours to be put onto study. This reduces the variability of the groups and allows us to decrease group sizes.

As part of initial characterisation of the models we will generate cell line and fragments determine whether we can generate transplantable models. This will reduce the requirement to specifically breed mice to support these experiments. Given potential numbers of mice that are wasted during the breeding of these complex models this has the potential to significantly reduce animal numbers.

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.

Only mice including transgenic are used on this licence. Using non-mammalian species is not possible since they lack the appropriate tissue structure and functional regulation. Therefore they cannot be used to predict exposure and efficacy in humans.

Animal condition will be monitored daily. Any mouse that exhibits 15% weight loss compared to peak weight for more than 2 consecutive days or 20% on any one day will be humanely killed.

Within this project we will use mice that had some of their genes edited in order to mimic cancer-relevant mutations and achieve the proposed scientific objectives. The most appropriate mouse models will be chosen based on previous in-house or external data for each model/project. In this project we are establishing models which aim to reflect the tumours seen in breast, ovary, lung, pancreas and prostate cancer. The models will be developed by two different methods.

One method is classically used in the literature, whereby mice are bred and aged, eventually developing specific tumours in the organs of interest. In some cases the tumours will be induced when mice reach adulthood. In >95% of cases the induction of the tumour will be via a non-invasive method. On very rare occasions it may be necessary to induce the gene by administering an agent directly to the target organ. This is only done when tumours may form more systemically if the induction is not done in a specific location. This will only be done when there is no alternative.

The alternate system is a novel method where mice are bred with a genetic alteration that by itself has no consequence. At a time of choice, a gRNA (tool for editing genes) can be administered to the organ of choice and when combined, these two tools will induce specific mutations and eventually tumours in target organs. This enables the development of multiple different tumour models from one breeding colony. For some tumour types it will be possible to add the gRNA via a non-invasive method that result in minor transient impact on the animal e.g. lung and breast models. For other target organs e.g. ovary, pancreas and prostate it may be necessary to administer the gRNA directly into the organ using surgery. We are working closely with a group that is looking at methods to reduce the requirement for surgery and where possible, surgery will be avoided.

It is believed that 10% mice on this licence will undergo surgery and each mouse will only undergo one surgical procedure. Surgery will be performed using aseptic techniques to minimise risk of infection. We will work closely with the vet and the named animal care and welfare officer to ensure the pain relief is optimal and the mice will be monitored more often until they are fully recovered from surgery.

Pilot studies will be performed to ensure that most refined endpoints are defined for each model. The most refined model that can be used to address the specific scientific questions will be used.

For all compounds profiled under this project licence tolerability in mice will have been confirmed independently. Where possible data will have been generated to confirm the doses used under this project licence are sufficient to induce a response in the relevant target (protein/cell type). This will ensure that the minimal adverse events are observed after compound administration and also that the level of compound is sufficient to achieve the scientific objective.

Where possible, very small blood volumes will be collected (microsampling) for downstream analysis, an approach that significantly refined the process of blood collection. Where appropriate, to reduce the number of animals used, multiple tissue samples will be taken from each animal to enable analyses of compound effects by different methods, from a single animal.