



Home Office

NON-TECHNICAL SUMMARY

Determining efficacy of novel cancer therapies

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, Pharmacodynamic

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.

The aim of this project licence is to develop therapies that reduce, inhibit or prevent the growth of tumours leading to new and improved cancer therapies.

Specifically the licence will be used to:

1. Investigate exposure and tolerability of new drugs and/or combinations
2. Develop new tumour models to test novel mechanisms
3. Profile novel therapeutic agents and/or combinations in tumour bearing models to investigate efficacy, development of resistance and support design of clinical dose and schedule.
4. Investigate target engagement of novel therapeutic agents ex vivo or in vivo in naïve animals
5. Investigate efficacy in inflammatory models to support novel immuno oncology targets
6. Profile novel therapeutic agents and/or combinations in tumour models where tumour develops within target organ

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?

By using targeted therapy approaches, the treatments should be more effective and should have significantly reduced side effects than those associated with current therapies. 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 60000 mice will be used over 5 years.

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 confirm the tumour types and compound doses are tolerated. In these studies we may observe weight loss and/or changes in clinical signs, such as social isolation or ruffled fur. 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. Depending on how the compound works, target engagement may be assessed in non-tumour bearing models. These models may require activation of an immune response and as such there may be transient signs of inflammation, including changes in behaviour. If these signs persist for longer than 4 hours then animals will be humanely culled. The majority of mice used on this licence will be used in tumour models where tumour grown superficially. Adverse effects related to tumour inoculation include brief discomfort or pain, but this will be minimised by application of good technique. The tumour types used are well tolerated and only two superficial tumour will be used per animal. Tumour size and condition is monitored closely on a daily basis. In some cases tumours will be implanted in organ of interest as this is more clinically relevant. We may observe weight loss and/or clinical signs as a result of tumour growth, but these will be minimised by applying early endpoints from pilot studies. The least invasive tumour site/line and earliest endpoints to achieve the scientific aims will be used. Animals will be culled if the tumour results in significant pain or distress. Animals will be dosed with compounds that have been shown to be tolerated. In some cases where tumour growth is slow or resistance is being monitored it may be necessary to dose mice for longer periods of time, but the number of doses an animal can receive will be within a defined limit and studies will not exceed 6 months in duration. 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. Animals where the immune-system is compromised will be housed in sterile conditions. 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 are used in the identification and selection of compounds and generally include measurements of the likely effect of the agent on the target cells. Activity in particular cell types however, cannot predict the likely *in vivo* activity given the complexity of issues such as bioavailability, metabolism and elaborate physiological interactions associated with tumourgenesis and therefore the whole animal is needed for the studies proposed in this licence.

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 all experimental design and analyses. Where applicable the following statistical guidelines will be used:

1. Statistical test defined in advance and optimised to ensure least possible animals are used that will result in meaningful results
2. Definition of meaningful biological change and measurable endpoints.
3. Estimates of biological variability used in sample size and power calculations.
4. Animals allocated in an optimal way based on estimates of biological variability established from historical data, pilot studies or published data.
5. Regular monitoring and updating of biological databases with regular review of group sizes.

An experimental protocol is written for each experiment including:

- a statement of the objective(s)
- a description of the experiment, detailing experimental treatments, the size of the experiment (number of groups, number of animals per group), duration of experiment, scientific endpoint

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 and immune-deficient strains, are used on this licence. Using non-mammalian species of lower neurophysiological sensitivity is not possible since they lack the appropriate tissue physiology. Therefore they cannot be used to predict exposure and efficacy in humans.

Within this project specific mouse strains or natural mutants are used e.g. nude mice. Genetically altered animals may be used in order to achieve the scientific objective. The most appropriate strain of mice will be chosen based on previous in-house or external data for each model / project. For human tumour lines immune-deficient animals are required to support the growth of the tumour, the least immune-deficient strain required to promote good, reproducible tumour growth will be used. The optimal conditions for tumour growth will be developed in pilot growth curve studies. Pilot studies to confirm tolerability will be performed on all compounds and combinations prior to progressing studies into the large anti-tumour efficacy studies.

The use of microsampling where possible has refined the process of collecting blood. Where appropriate, to reduce the number of animals used, multiple tissue samples for PD analysis will be taken from each animal.