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NON-TECHNICAL SUMMARY

Preclinical evaluation of cancer therapeutics

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 following aims mentioned in paragraph (b)

Key words

Cancer, Therapy, Immunotherapy, Pharmacodynamics, Efficacy

Animal types	Life stages
Mice	Adult

Retrospective assessment

> The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

The purpose of this project licence is to deliver a high-quality, need-based service that tests how well new cancer treatments work and how safe they are, using established mouse models 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.

Why is it important to undertake this work?

Although treatments for some cancers have improved a lot over the last 20 years, cancer is still the leading cause of death worldwide, accounting for nearly 10 million deaths in 2023, according to the World Health Organisation (WHO).

Most cancer treatment still depends on surgery, radiotherapy, and chemotherapy, which can cause serious side effects and sometimes long-term health problems. In recent years, immunotherapy has changed cancer treatment by helping some patients live longer, especially when other treatments have not worked well. However, it does not work for everyone, some cancers become resistant to it, and it can also cause immune-related side effects. Therefore, there is still a strong need to develop cancer treatments that are safer, work better, and can help more patients.

The work proposed under our license will provide data to companies to help them apply to test new drugs in people and guide early decisions on whether a drug is worth developing further. The overall aim is to find better treatment options for people with cancer.

What outputs do you think you will see at the end of this project?

There is a need for new cancer treatments because the disease sometimes come back (relapse), stop responding to existing treatments, and many patients experience long-term side effects.

The aim of this project is to provide data from animal models of cancer to biotech and pharmaceutical companies to find drug candidates that are most likely to help patients and to flag any that show little benefit or dangerous side effects so they can be stopped or redesigned as early as possible.

After each study, we provide a detailed report with information about how well the new drug worked against cancer and how it worked in the body. This report also includes recommendations of how/if to proceed, which helps companies decide which drugs to develop further and how they are best given to patients, including the right dose and timing.

We will also, where appropriate and permissible, share data with the wider scientific community, through presentation at relevant scientific meetings and publication in peer-reviewed, open-access journals.

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Who or what will benefit from these outputs, and how?

Primarily, the scientists who have developed new therapeutic strategies and agents for cancer will benefit from being able to make decisions about research priorities. The wider research community pursuing similar goals may benefit from what we find out (within the lifetime of the project), by making appropriate choices of experimental models or therapeutic approaches; for example, based on findings that may be presented or published by ourselves or our collaborators. Ultimately (although not within the lifetime of the project), it is hoped that people suffering with cancer will directly benefit from the output of the studies that we have been part of, with the availability of new treatments.

By making better decisions early on, fewer drugs fail later in clinical trials, which saves time and money. It also means fewer unnecessary animal studies (often in species such as dogs, pigs or monkeys) and studies using human volunteers and it also lowers the risk of side effects caused by incorrect dosing. Most importantly, this work helps the development of better, more effective cancer treatments.

How will you look to maximise the outputs of this work?

The information we provide to the industry is as extensive as we can provide, from in-life parameters showing efficacy of the drug, to analyses of tissues post-mortem that will help confirm the mechanism of action of the drug and perhaps identify biological molecules that may represent a response to therapy. With this data, we aim to support our clients to progress their drug into clinical trials and, in the longer term, be of benefit to patients as a standard of care.

As a contract research organisation we are limited in what we can publish, as the data we produce belongs to the company who contracts us, but clients are encouraged to publish whenever possible. That being said, data from animal studies that we have performed have been included in at least a couple of publications during the last 5 years and we often present our development work at international conferences.

Species and numbers of animals expected to be used

- Mice: 4200

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

Explain why you are using these types of animals and your choice of life stages.

The programme requires that models are used which closely mirror the human disease situation. Adult mice are suitable for these studies as the work cannot be conducted in lower vertebrates, invertebrates or cell lines due to the poor resemblance of these options to what actually happens in a patient with cancer.

Typically, what will be done to an animal used in your project?

On arrival the mice, which are often immunocompromised, are placed in individually ventilated cages, given irradiated diet (if immunocompromised) and allowed to settle into their housing for at least a week. They may then receive test drugs to check safety, how the body processes the drug, or how well it works against cancer. Animals are monitored closely throughout.

To establish locally growing tumours, human or mouse cancer cells will be injected under the skin of the mouse. To establish systemic disease (cancer that can spread to other organs in the body), human or mouse cancer cells are injected into the organ where that cancer normally grows (i.e. brain cancer cells will be implanted into the brain) or directly into the blood stream so that the cancer can spread. If human cancer cell lines are used, it is essential that the mouse strain is immunocompromised, to allow the tumours to establish. Some procedures require brief anaesthesia and pain relief. Animals are checked regularly to ensure they remain comfortable.

During studies, animals may experience regular injections under the skin (subcutaneous administration), into the abdominal cavity (intraperitoneal administration) or into the tail vein (intravenous administration). Some mice may receive treatment orally via a feeding tube. Mice may have small blood samples taken via a tail vein bleed on a weekly basis. Some animals may undergo short imaging sessions under light anaesthesia and some may receive sub-lethal irradiation (radiotherapy). All procedures use methods known to be well tolerated.

Studies end at a planned timepoint or if an animal reaches a welfare limit. Animals are then humanely euthanised under anaesthesia so tissues can be examined. Most studies last one to three months.

What are the expected impacts and/or adverse effects for the animals during your project?

Adverse effects after test item administration may be weight loss and diarrhoea. Less frequent adverse effects may be bruising, anaemia, reduced movement, grooming and postural changes. Infrequent adverse effects may be abnormal breathing, tremors, convulsions and reduced peer interaction.

When tumours are implanted under the skin, animals may feel brief discomfort from the injection. Tumours may sometimes show signs of ulceration.

In cancer models where tumours grow inside organs (orthotopic or metastatic models), effects depend on the site. These may include weight loss, weakness, enlarged organs, fluid build-up in the abdomen, bone pain, or neurological signs such as imbalance or unusual movements.

Animals receiving whole-body irradiation may lose weight.

Throughout all studies, animals are monitored closely so that any signs of pain, distress, or illness can be identified early and managed promptly.

Expected severity categories and the proportion of animals in each category, per species.

What are the expected severities and the proportion of animals in each category (per animal type)?

The expected severity for mice under all protocols under this licence is moderate. This is based on previous experience obtained under project licences involving closely related studies and comparable experimental procedures.

What will happen to animals used in this project?

- Killed

Replacement

State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.

Why do you need to use animals to achieve the aim of your project?

This project needs to use models that behave as closely as possible to real human disease. Studies in animals can answer important questions that current laboratory (in-vitro) tests cannot, such as how safe a new treatment might be, how the body absorbs and processes it, and what effects it has throughout the whole body. These “PK/PD” studies look at how a drug moves through the body, how long it stays there, and what it does while it is there.

Animal studies are also needed because cancer develops and responds to treatment differently in a living body than it does in a dish. Using animals allows researchers to study cancer in an environment that is much closer to what happens in patients.

Which non-animal alternatives did you consider for use in this project?

It is anticipated that any new drug evaluated under this licence will first have undergone appropriate laboratory testing to establish a clear scientific rationale to move to animal studies. These studies may have been conducted using validated in vitro models within our laboratory (see below) or by external collaborators or sponsors before the drug is submitted for testing. Where appropriate, additional non-animal approaches, such as computer modelling and studies using non-protected species (e.g. fish, where permitted), may also have been used to assess biological activity and identify potential safety concerns before progression to animal studies.

Sponsors are required to provide comprehensive information for each proposed study, including the scientific rationale, details of the investigational drug, and all available data on its biological activity, efficacy, and safety.

Only agents that demonstrate promising activity against their intended target, together with an acceptable safety profile and minimal effects on healthy cells or tissues, will be considered for in vivo testing.

We have validated 2D tumour models, where cancer cells are growing in thin, flat layers on a plastic surface, and 3D tumour models, where the cancer cells grow like clumps or structures that mimic how

tumours form in the body, to test how well new drugs work. Some cancer cell lines can form "ball-like structures" (spheres), which resemble solid tumours that often have a core and an outer layer. We can use these spheres to test new drugs and to see if the drug can reach into the core of the sphere or if it only kills the outer layer of cells.

More recently, we have focused on creating 3D intestinal “mini-organs” (organoids) grown from tissue samples from a range of species, including humans, mice and rats. The organoids, that mimics the structure and function of a real organ, allow us to test potential drugs in the lab and identify which ones are likely to be the safest and least toxic before moving forward with further studies. However, there are still many components to be introduced to these models, such as immune cells and other tumour infiltrating cells, to better mimic the human disease state.

We are continuously working to improve existing non-animal research models while also exploring innovative approaches that may provide new ways to address our scientific questions without the use of animals. We conduct regular searches for relevant non-animal methodologies using scientific databases such as the National Institutes of Health’s PubMed. Our searches include terms like “alternatives to animal testing” and “in vitro cancer models,” helping us remain up to date with emerging technologies and established non-animal approaches. We also, follow the Replacement Checklist provided on the Replacing Animal Research webpage to try and ensure that all possible non-animal options are carefully considered and evaluated as part of our research process.

With time there will be a progressive accumulation of data that will allow us to compare the outcomes we observe in the cell culture models to those we see in the animal models. The ultimate goal will be to replace, where possible, the need for animal studies.

Why were they not suitable?

All compounds tested under this licence have previously been evaluated using available and appropriate non-animal technologies before in vivo testing would be considered as the only option for further development. These include studies that demonstrate the mechanism of action (eg. regulation of proliferation, induction of cell death, target cell specificity). Their limitations are, that although they allow assessment of test items on specific aspects of the disease process, they are insufficient in modelling the complex interaction of the different cellular systems present within an in vivo tissue.

Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.

How have you estimated the numbers of animals you will use?

The number of animals quoted is based on animal usage over the last 10 years. A similar level of work is anticipated for the coming five years.

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What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

The most important aspect of the proposed programme of work, which will reduce the overall number of animals used, will be to carefully select and only take forward the most promising treatment targets. This will be done by firstly studying these targets using laboratory tests on cells and/or tissues. This along with any existing data from animal studies, will be used to assess whether a target is likely to lead to useful new treatments. Work may be turned down if there is not enough strong laboratory evidence to support a target. In vivo models will not be used for random compound screening and all experiments will be hypothesis led. All experiments will be conducted following standard operating procedures and include appropriate controls, so that the efficacy of test items can be accurately assessed. The number of animals used will be the minimum number required to test the experimental hypothesis at the required level of statistical power and significance. We regularly consult academic and commercial statisticians. For example, data produced under the previous licence have been reviewed and the suggestions for improved analysis have been included in this licence application.

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?

Several of our tumour models utilise imaging, which helps reduce animal numbers as the progression of disease can be followed in the same animal over time. We regularly seek statistical consultancy, sometimes providing historical data, to ensure that our power analyses are correct for each model we offer. Internal expertise in tissue analyses, allows us to fully characterise the cellular changes associated with disease as well as the expression of key factors on the surface of tumour cells and surrounding cells. This information is utilised to refine existing/validated models so that the most appropriate model is chosen to test a compound’s mechanism of action.

Centralising the use of these models results in a greater level of assay standardisation, reducing the number of studies performed. We are exploring the possibility of sharing control data between studies to further reduce animal use, where allowed.

Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

To test the treatment effects of novel anti-cancer drugs it is necessary to induce sufficient levels of disease. Some studies will be performed in immunocompromised (having a weakened immune system) mice. More severely immunocompromised mouse strains may be required for some tumour models and sometimes mice may be humanised (mice that carry some aspect(s) of human biology).

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We will predominantly use subcutaneous (tumours grow under the skin) cancer models in mice. Animals will receive treatment delivered by an appropriate route of administration and the tumours are measured 2-3 times a week.

We may also use cancer models where tumours grow inside organs (orthotopic or metastatic models). These models are often imaging-based where the cancer cells can be tracked over time in the same animal using imaging. The endpoint for several of these models is now based on imaging signal rather than humane endpoints, reducing suffering.

In some cases, we may use tumour models in mice with a normal immune system (syngeneic tumour models in mice). These models are mostly used to test immunotherapies where a fully functional immune system is needed to test how treatments interact with it.

In general, the models used under this license are refined and designed to mirror the human disease situation whilst causing the least pain, suffering and distress to the animals.

Why can’t you use animals that are less sentient?

Tumour growth must be studied in a living animal with a fully functioning circulatory system, allowing both the body and the cancer to receive oxygen, nutrients, and other essential factors as they would in a human cancer patient. Hence, it would not be appropriate to use animals that have been terminally anaesthetised. In addition, because cancer in humans predominantly develops during adulthood, it would not be suitable to use younger mice.

Mouse models are the best characterised of all experimental oncology models. This project requires that the models used are ones which closely mirror human disease so that we can address the development and treatment of cancer in an environment which is the closest to the microenvironment found in cancer patients. Hence, this work is not suitable to be conducted in lower vertebrates, invertebrates or cell lines due to the poor resemblance of these options to what actually happens in a human cancer patient.

Rodents provide a cost and time effective platform for most pre-clinical testing. For the purposes of oncology testing, the use of higher species is not required because there is a wealth of knowledge on different types of cancer in rodents, as well as decades of in-house expertise with such models.

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?

Animal welfare checks are performed at least once daily and clinical observations are recorded. Data are reviewed daily to assess if any intervention is required. At defined points in the study mitigations such as analgesia and increased frequency of observations are introduced. When animals are recovering from anaesthesia, they are monitored carefully and analgesia is given if they have had surgery to minimise pain. The NC3R guidelines will be followed with regard to best current practice for blood sampling and administration of substances to the animals.

The mice are maintained in an enriched environment designed to support their welfare. Wherever possible, they are group-housed because mice are social animals and isolation can be stressful for

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them. They are also provided with nesting materials, hiding places such as paper tubes, and wooden sticks to encourage natural gnawing behaviour.

During the project, we will operate a process of continuous review to ensure that the models we run are fit-for-purpose. This involves looking at all the data that we collect and seeing how it may change with time. We can then make appropriate changes to ensure that the models we run are the most refined, minimising the pain, suffering and distress of the animals.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?

We will perform procedures according to our own standard operating procedures which are based on the PREPARE guidelines for the planning of animal research to support high standards of animal welfare and scientific quality. We will also follow the guidelines published by Workman P et al. (2010). Guidelines for the welfare and use of animals in cancer research. Br J Cancer 102(11):1555-1577 and guidance from the NC3Rs, as appropriate.

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?

There is a local 3Rs manager available for consultation. We are staying informed about the 3Rs advances through attendance at lectures and seminars run locally, and we regularly getting informative emails from the NC3Rs. We are keeping up to date with the literature within the field of pre-clinical cancer research and are actively looking to implement refinements to our models. Our standard operating procedures are reviewed on a regular basis to accommodate refinements.

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