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NON-TECHNICAL SUMMARY

Development and evaluation of anti-cancer agents and combinations using pre-clinical rodent cancer models

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

Cancer, Tumour, Therapy, Efficacy, Biomarker

Animal types	Life stages
Mice	Adult, Aged animal
Rats	Juvenile, 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 aim of this project licence is to identify potential drugs / therapies that reduce, inhibit or prevent the growth of tumours, leading to new and improved cancer treatments.

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?

Cancer is a leading cause of death worldwide. With an estimated 20 million new cases of cancer recorded worldwide in 2022, accompanied by 9.7 million cancer deaths, research into new treatments is now more important than ever. Within the UK, there were 346,217 new cancer cases diagnosed in 2022, with the four most common cancer types being lung, bowel, breast and prostate.

Despite recent advances, there is still a need to develop more effective anti-cancer therapies and combinations that target and treat the disease in novel ways. Patient quality of life is an important consideration when developing new cancer treatments that are specific, effective and safe. Many current cancer therapies have side effects that negatively impact patients and their lives, meaning it is important to try to develop new treatments with fewer side effects so patients can stay healthier during treatment.

Through our research we seek to eliminate cancer as a cause of death by developing new treatment options that aim to kill cancer cells to help patients live longer. Our focus is on some of the most aggressive and hard-to-treat cancers including pancreatic cancer, certain blood cancers, and cancers within breast, lung, ovarian, and prostate. Through our research programs, we investigate cancer treatment options from different angles, including using the immune system to fight cancer, targeting proteins which cause cancer and resistance to therapy, targeting the proteins that control cell replication, novel treatments that take the drug to the cancer cells, and targeting proteins that control gene expression. These targeted approaches to developing new cancer therapies aim to improve patient quality of life while undergoing treatment in addition to helping patients treat their cancer and live longer.

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

The benefit of this project will ultimately be the introduction of new and improved treatments for the management of cancer.

This project will establish new rodent models of cancer and potentially new assays for assessing treatment effect.

Novel findings will be published in high impact journals, with the aim to publish approximately 15 scientific papers from the animal studies completed during this project.

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

Since our approaches are applicable across a broad range of tumour types, it is hoped that the drugs developed from this project licence will have wide utility across different cancer patient populations. These may not completely cure cancer patients, but it is expected that they will enable a significant number to live longer by stopping or slowing the growth of their cancer. As well, through the development of more targeted drugs, patients should experience fewer side effects and therefore have an improved quality of life following the diagnosis of this devastating disease.

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

New information will be disseminated at key national and international conferences via poster sessions and seminars. Publication of both successful and unsuccessful data in relevant journals will occur. We will share pre-clinical animal data with principal investigators to influence clinical trial designs. We work in collaboration with many scientists and groups in which we are able to share data and learning, meaning that important data generated from our animal studies can be shared more widely to avoid others repeating work and to help influence other areas of animal use.

We will share good practice with external animal welfare groups and also internal teams conducting animal studies.

Species and numbers of animals expected to be used

- Mice: 71,250
- Rats: 3,450

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.

We use animal studies in mice and rats alongside many other experimental approaches and they are crucial in building up a complete picture of cancer biology. Our research using animals has helped drive advances in cancer treatment that are benefiting people with cancer all over the world today.

Our work mainly uses mice (90%), which can grow tumours which mimic those of human cancer patients. Studies of cancer in mice mimic the complex way tumours grow and spread in people with

cancer. The majority of our work involves implanting a tumour on the side of the animal. Although this is unlike the patient situation, the use of these models over the years has demonstrated utility in selecting viable drug candidates. The majority of studies use cancer cells that are derived from human tumours. As the human tumour tissue is foreign to the animal, the animal's immune system would reject the tumour tissue and therefore we need to grow human tumours in either mice or rats that have an impaired immune system. This allows the tumour tissue to grow and not be rejected.

Mice can be easily genetically altered to allow us to study the genetic causes of cancer and reproduce tumour types which naturally occur in humans in the correct tissues and body systems.

We also conduct some studies in rats (10%). Some compounds that we need to test may not have sufficient levels in the blood of mice to have an effect on the tumour and therefore we need to use the rat as an alternative species. The rat is also usually the species of choice for toxicity studies. These studies would be conducted under a different project licence but it may be necessary to directly compare the dose level of a drug that causes an effect on the tumour to the dose level that produces unwanted side effects. This is to ensure that there is a big enough margin between activity and safety in order to progress to the clinic.

In some instances cancer growth can be influenced by hormones; these are classed as hormone-sensitive tumours. It may be necessary to run some experiments in rats that do not have high levels of circulating hormones and in these instances rats that have not yet become sexually mature will be used. For this type of study, juvenile rats are imported and are weaned before study start. They are classified as adult rats when they begin the study.

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

The rats and mice we use are bred at specialised facilities and are then transported to our facility. We primarily use breeding facilities within the UK but on rare occasions specialised strains may be required to be imported from within the EU or USA. Animals will be transported in safe enclosed boxes that contain bedding, food, water and are maintained throughout the journey within temperature and humidity levels appropriate for the species. Upon arrival to our facility the mice or rats are transferred into clean cages. Animals are left to get used to their new home surroundings for at least 7 days before any experimental procedures are performed. In our facility the cages are Individually Ventilated (IVC) and each cage has its own clean air, food and water supply. In addition, bedding and nesting material and numerous forms of enrichment are included. The cages are maintained at the appropriate temperature and humidity for the species. Cages are changed at least once every two weeks and water and food is checked daily.

Mice and rats are typically housed in small groups as they are social animals. On occasions animals may be singly housed *e.g.* in situations where male mice naturally fight with each other, they may be housed singly for welfare reasons. During an experiment, animals in different treatment groups must be housed separately. In situations where only one animal is left in a treatment group, but is still providing valuable data, that animal may need to remain on its own until the study is finished.

In a typical study, animals are placed under anaesthesia and have a microchip for identification inserted under the skin. At the same time, they are also injected under the skin on their side with cancer cells which grow into tumours. In some cases the tumour is not available as cells and therefore

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a very small piece of tumour tissue needs to be put into this area surgically. The mice or rats would be anaesthetised as this requires a very small cut in the skin so the tumour tissue can be placed under the skin. The cut is then closed using either stitches, special glue or clips.

Sometimes tumour cells require the presence of hormones, such as oestrogen, in order to grow. When required, we supply these hormones to the animals in their drinking water, or sometimes through small pellets that we place under the skin via a minor surgical procedure. For cancer types where the patients have low levels of specific hormones, we mimic this in our cancer models by neutering the animals (removing testes or ovaries) via a surgical procedure.

In some cases, tumours may be grown within the organ of interest (*e.g.* lung, breast, prostate, pancreas). This may either be via direct injection of cells into the organ or the use of genetically engineered mouse models. The injection of cells into the organ of interest may require surgery to allow direct injection into the organ, or injection of cells into the tail vein. The least invasive way of administering the cells will be used. Genetically engineered mouse models use mice where mutations seen in the clinic are induced in the target organ. Where tumours grow within the organ of interest, tumour burden may be monitored by non-invasive imaging methods (*e.g.* fluorescence detection or high resolution imaging) under anaesthesia. Animals will be closely monitored for any clinical signs that may relate to the tumours growing (*e.g.* changes in breathing pattern).

In these studies, once the tumour has started to grow, the animals will start to receive doses of a potential anti-cancer drug, combination of agents, or a relevant control. Anti-cancer drugs are usually dosed orally using a narrow, blunt dosing tube, or into the abdomen using a needle, and the animal may typically receive two or three doses per day for 28 days. On rare occasions, when continuous administration of the test substance is required, a small slow release device may be implanted surgically under the skin. All animals are closely observed every day and bodyweights and condition of the animals are recorded to ensure that the animals are not unwell. Animals will be closely monitored for any effects that may relate to treatment dosing (*e.g.* change from normal clinical condition). An off-treatment tumour re-growth period may be required.

Sometimes, we also administer an agent that modifies the action or effect of the potential anti-cancer compound, so that we can study it effectively in animals. For some compounds, we are able to asses their effect by looking at specific changes in blood and/or other tissues/organs, which means we can test these agents in animals without implanting a tumour.

During the study blood samples may be taken from a vein. Hair follicles may be collected, and/or small tissue samples may be taken from the tumour using a specially designed fine needle, while the animal is under anaesthesia.

A mainstay of cancer treatment in the clinic is radiotherapy, so some animals may be treated with irradiation alone or in combination with anti-cancer agents.

On some occasions, animals may be re-used to maximise the data collected from the animals without substantially increasing the harms they experience. An example is when injected cancer cells do not grow as expected, so we cannot achieve the original study aim, but we are still able to assess other useful endpoints. Animals being re-used will only have experienced limited procedures (such as identification and cell implant under anaesthesia) before re-use.

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In rare circumstances, animals may be required to remain on study for an extended period of time, typically no longer than 1 year. At the end of the study the animal is humanely killed and the tumour tissue and other tissues may be taken which can then be used for further investigation.

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

One particular strain of immunodeficient mice (NSG) used in this project may show swelling around the hocks in 10-20% of animals. Any animals experiencing swelling around their hocks may be given an altered enrichment, pain relief and/or anti-inflammatories in consultation with welfare- and/or veterinary-trained experts. One particular strain of immunodeficient rats used in this project may show altered breathing in 5% of animals. If observed, the rat will be humanely killed.

Animals undergoing surgical procedures, such as neutering, will be given pain relief. Minor, transient swelling and bruising at the surgical site may be expected, along with mild bodyweight loss, but these effects are expected to resolve within a few days of surgery.

Some animals develop small scabs or wounds at the site of microchip insertion on the scruff, however these typically show signs of healing within a few days.

Animals will develop small tumours following implant/induction; these will continue to grow and will be monitored regularly. Tumours on the flank do not appear to cause the animal any pain or discomfort and the animals continue to behave normally. Small scabs on the surface of the tumour may form but do not typically impact animal behaviour. If the scab opens, the animal will be humanely killed. Tumours that grow in the organ of interest may cause deviations from normal behaviour, such as altered respiration rate. The size the tumour can grow to is limited by the use of a measurement and/or animal clinical condition scoring system to ensure that it does not cause any lasting pain or discomfort to the animal.

Animals who are given oestrogen to help tumour growth may experience skin lesions, which we monitor closely and can treat with agents such as petroleum jelly. Administering oestrogen in drinking water may alter the taste of the water and reduce water consumption, leading to dehydration. This is minimised through the use of palatability enhancers such as sucrose or sweeteners.

The dosing procedure used for giving the anti-cancer agents, including slow release devices under the skin or irradiation, does not usually cause any issues, but the treatments themselves may have some side effects. Side effects may include weight loss, clinical observations, and/or abnormal behaviours such as being less active or not socialising or interacting with their cage mates. Strict criteria are put in place to minimise any unwanted effects and to minimise any pain, suffering or distress to the animals, so that any side effects only last for a short period of time.

Occasionally, as a result of taking a small blood sample, or small tumour sample with a specially designed fine needle under anaesthesia, some animals may experience mild and transient bruising and/or swelling near the sampling site. As a result of the tumour sampling procedure, the mice may also have a small wound from the entry/exit of the needle.

Repeated exposure to anaesthesia may alter normal behaviour or extend recovery times. Aging of animals and single housing may lead to changes in animal behaviour.

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Some inducing agents, such as doxycycline, may have adverse effects, which may include skin flaking.

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)?

Mice: Mild 10%; Moderate 90%.

Rats: Mild 10%; Moderate 90%.

What will happen to animals used in this project?

- Killed
- Kept alive at a licensed establishment for non-regulated purposes or possible reuse

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?

To help us achieve our project aims, the use of animal models is indispensable. They allow us to study and understand the complex mechanisms that underpin cancer, particularly tumour growth and metastasis, within a whole living organism. Understanding these systemic processes is crucial for advancing new diagnostic and therapeutic methods. Additionally, animal studies ensure the safety and efficacy of potential treatments before testing these new therapies in human patients. Animal studies are conducted only after all feasible tests on cancer cells in the laboratory have been exhausted and where no alternative exists.

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

We explored several non-animal alternatives, including:

‘Organ-on-a-Chip’ technology uses a special chip containing channels that are lined with growth matrix and the cell type of interest. These mimic real human organs. Test agents flow through the channels and we can assess the interaction between the treatment and the cells. The organ-on-a-chip is designed to mimic some organ functions and interactions using human-derived cells rather than testing these processes in live animals.

A small amount of tumour or organ originally from either humans or rodents can be used to test the effect of our drugs on the tissue within the laboratory setting. This approach can be used for observing specific cellular responses and interactions outside of the living organism. When animal cancer cells are used, this is a partial replacement of an intact animal.

Human and mouse cancer cells grown in the laboratory can be used for the initial assessment of test agents. This technique looks for expected and unexpected changes in cell proteins. When animal cancer cells are used, this is a partial replacement of an intact animal.

Why were they not suitable?

While promising, these alternatives currently do not meet our research needs:

Organ-on-a-chip and laboratory-grown tissues lack the reliability and comprehensive multisystem integration seen in rodent models. They cannot replicate the full physiological and immune responses crucial for understanding cancer progression and treatment.

The assessment of treatment levels in blood and the effect of the treatment on the tumour are essential for our project aims. The above alternatives do not provide a suitable replacement for assessing drug absorption, distribution, metabolism, and excretion in a living system.

Cancer cells grown in the laboratory do not capture the complex interaction of biological systems required to predict drug responses in humans accurately. Thus, rodent models remain the most relevant and comprehensive choice for our research objectives. However, we use cell testing extensively to screen thousands of potential compounds, and significantly narrow down the number of compounds progressing to animal experiments to only a small number of promising candidates.

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?

This licence reflects a well-established cancer research program, and the numbers of animals used within this project licence are based on the diverse areas of cancer that are being investigated. We often are trying to develop drugs for up to ~30 novel tumour targets at any given time. Each novel approach requires multiple studies per year to identify the most promising treatment agents. We typically run approximately 20 studies per month, with each study using approximately 120 animals. Conducting studies of this size allows us to use a single control reference group to test and compare the activity of multiple compounds simultaneously. If these compounds were tested in separate studies, these treatment comparisons would not be possible and each study would require its own control group, ultimately using more animals overall.

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

Our studies are meticulously designed to ensure minimal animal usage while effectively addressing the scientific questions posed. We utilise the expertise of a statistician to analyse data and predict outcomes, thus optimising our designs to detect effects with the least number of animals needed without compromising the integrity of the results.

All experiments are conducted in accordance with our local good practice standards that are established by a regulatory compliance team, and are designed to ensure accuracy, reliability, traceability, and reproducibility of data. Additionally, our studies meet regulatory authorities' legislative requirements.

Research planning follows the PREPARE guidelines, ensuring excellence in the planning and execution of animal experiments.

For example, to ensure we do not bias our findings, we do not put all the largest tumours or smallest tumours into the same treatment group. Instead, tumours are allocated to different groups so that the average tumour start size of each group is similar. This reduces the chance of tumour start size biasing the outcome.

Publications comply with the ARRIVE guidelines, maximizing the clarity and quality of reporting.

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

When different project groups wish to investigate their compounds using the same tumour model, we consolidate studies to share control groups, thereby reducing repetitive usage of control groups when feasible.

To mitigate the side effects associated with anti-cancer compounds, small pilot studies involving 2-3 animals are conducted to identify any unwanted effects before expanding to larger cohorts.

Wherever possible, multiple tumour and/or tissue samples are taken from the same animals, utilizing frozen samples in further non-animal experiments. In instances where tumours fail to grow as expected, animals may be transferred to different protocols to assess non-tumour endpoints. For example, animals which were implanted with tumour cells that have grown atypically may be transferred onto another protocol to evaluate target engagement within other tissues following treatment, which may reduce the need for further studies, thus minimising additional animal usage.

Some studies incorporate dual flank tumour models where feasible, allowing each mouse to host two tumours instead of one, reducing the overall number of animals required.

For breast cancer models, injecting cancer cells through the nipple into the mammary tissue under anaesthesia has shown improved tumour growth consistency compared to subcutaneous methods. This has the potential to reduce animal numbers per study while maintaining animal welfare.

We also use pilot studies to test whether new tumour models grow in a consistent manner. The outcome of these pilot studies is carefully reviewed to optimise the number of animals used in the project. Only tolerated compounds and reproducible tumour models are subsequently used to evaluate the effect of potential anti-cancer drugs.

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Where feasible, mixed-sex groups are used in studies with genetically engineered mouse models to minimise breeding requirements. We also generate cell lines from tumours to reduce breeding needs.

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.

We will use a wide variety of different tumour models in both mice and rats. The majority of the tumours are implanted as cells in an area on the animal (the lower right side of the back (flank)) which allows the tumour to be easily monitored and measured and does not affect the animal's ability to move around. The size the tumour can grow is limited to ensure that they do not cause any pain or discomfort to the animal. For some potential anti-cancer drugs, it may be possible to test activity in animals without a tumour by assessing changes in biomarkers in blood or normal organs.

In some instances (<10%) it may be required to grow a tumour in the organ where the tumour was originally derived from, for example a breast tumour implanted into the breast tissue. The tumour may be assessed using imaging and/or other monitoring methods which can track the tumour growth. For appropriate models, we develop scoring systems to monitor animal welfare.

All new tumour models are first tested in a small number of animals (typically 5 to 10 per group) before being used in larger numbers of mice. When a new tumour model has been established, we limit the number of animals used in the first study (typically to ~60 mice) to give us an opportunity to ensure the model growth and endpoints are robust, before using the model in large numbers of animals.

The dosing procedure for the administration of the anti-cancer agents does not usually cause any issues, but the test agent itself may have some side effects. Side effects may include weight loss or abnormal behaviours, such as being less active or not socialising or interacting with their cage mates. The test agents are tested in a very small number of animals initially (typically 2 to 3 per group) and only substances that do not have unwanted side effects can be used in larger numbers of animals.

It may be necessary to surgically neuter animals to reduce levels of hormones as the growth of some tumour models may be influenced by hormone levels (hormone-sensitive tumours). Any animals that undergo a surgical procedure will be provided with pain medication prior to the surgery and maintained in a warm environment until fully recovered to minimise weight loss. Pain medication may be administered after surgery.

When establishing new tumour models in rats, where possible, we will use strains of rats that are sufficiently immunocompromised without the need for whole body irradiation to further suppress the immune system.

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

Using less sentient animals, for example a non-mammalian species such as the fruit fly, is not possible since they lack a closed circulatory system, which means you cannot replicate a number of the complex processes that are involved in cancer such as the growth and spread of tumours.

Juvenile life stages of vertebrates such as zebrafish is a developing option, and early attempts to implant human tumour cells into zebrafish have shown promise for tumour inhibition studies for testing new agents. These models rely on protected life stages of zebrafish, and may need larger numbers, although moving to a vertebrate considered less sentient than a rodent may be a possible refinement in future. However, the small size of zebrafish makes it challenging to collect meaningful blood samples. Being able to measure blood concentrations of our compounds is an essential part of our work and allows us to be able to calculate doses to humans. Therefore, it means that zebrafish models are not currently practical, and rodent tumour models remain the most effective option at present.

Others have investigated embryo larval life stages of zebrafish that would be unprotected within the EU (since they work before the day 5 threshold of protection) with some success, but as above, the ability to measure blood concentrations of our agents and administer precise doses remains the challenge in this case as well due to the small size and blood volume of the zebrafish.

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

All animals will be acclimatised for 7 days from arrival before they undergo any experimental procedure.

Enrichment provided such as paper houses, tunnels and chew sticks allow the rats and mice to have improved welfare and demonstrate natural behaviours such as sheltering, nesting, climbing and gnawing.

We closely follow and implement the latest welfare guidelines from our animal welfare group, and therefore handle animals using non-aversive methods that cause the least amount of harm or stress to them as possible while conducting these experiments.

Any NSG mice experiencing swelling around their hocks may be given an altered enrichment, pain relief and/or anti-inflammatories in consultation with the Named Animal Care and Welfare Officer (NACWO) and/or Named Veterinary Surgeon (NVS).

All surgery is performed in concordance with 2017 LASA Guiding Principles for Preparing for and Undertaking Aseptic Surgery.

The use of microchips provides unambiguous identification of animals and links directly to our data capture software to reduce typographical errors. We have generally adopted the workflow of purchasing our mice pre-microchipped at the supplier, so that the mice have a period of low handling after microchipping to avoid disrupting the healing process. This has significantly reduced the likelihood of small scabs developing at the site of entry of the microchip.

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We can provide a bolus administration of saline for compounds known to cause dehydration to minimise associated weight loss.

When administering substances via the IP route using a daily or twice daily schedule, doses will be administered into alternating sides of the abdomen whenever possible.

Wherever possible, we adhere to a single needle use policy.

We will follow the local guidance for Tamoxifen use whenever relevant.

For some substances, including test substances, hormones, and inducing agents, it is possible to administer them in the diet or drinking water and this has the potential to reduce animal handling in chronic dosing studies. If administering these substances via drinking water, we can potentially also add sugar or sugar-free cordial to the water to camouflage the taste so the animals continue to drink a normal amount and are less likely to experience dehydration.

We have been exploring the establishment of oestrogen-dependent breast cancer models which do not require additional oestrogen supplementation. For example, growing some breast cancer cell lines in the mammary glands, via intraductal administration, has been shown to remove the need for supplemental oestrogen administered via a surgically implanted slow release pellet. For tumour models that still require oestrogen supplementation to support growth, we are continuing to try to supply the hormones via drinking water rather than via surgical implant of an oestrogen pellet under the skin. Administering hormone in drinking water not only avoids a surgical procedure, it can also reduce the frequency of oestrogen-related side effects (body scalding) in the animals.

Welfare scoring tables will be established for novel models where tumours grow in the organ of interest. This allows us to ensure our endpoints are the most refined possible. The aim will be to design the experiments to occur over a timeframe that avoids the animals developing an accumulation of adverse clinical signs. Where possible we will include the use of imaging to facilitate earlier humane endpoints.

When serial core needle biopsy samples are planned, we will ensure that any swelling has resolved, no open wounds are present, and any mild bruising is showing signs of healing before a subsequent sample is attempted. Serial samples will be collected from different sites on the tumour whenever feasible. As we build our experience with different tumour models and mouse strains, we will look to develop guidance for biopsy sampling suitability, in collaboration with the NACWO/NVS.

We have developed posters with images of different tumour conditions (*e.g*. red, pale, lesion) to aid in monitoring and applying appropriate endpoints based on the appearance of the tumour.

All animals will be housed in specialised cages. These cages are Individually Ventilated Cages (IVC's) which filter the air and fully protect the animals from micro-organisms. All food, water and bedding is also fully sterilised beforehand. All cages have various forms of enrichment included, for example a cardboard house, sizzle nest, tunnels, chew stick. Where possible, the enrichment is alternated on a regular basis to benefit the animals. The temperature and humidity is kept within a specified range that is optimal for the animals.

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

Guidelines for the welfare and use of animals in cancer research (Workman, P., Aboagye, E., Balkwill, F. et al. Br J Cancer 102, 1555–1577 (2010)).

Animal research: Reporting in vivo experiments: The ARRIVE guidelines. Br J Pharmacol. 2010 Aug; 160(7): 1577– 1579.

Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, et al. (2020) The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. PLoS Biol 18(7): e3000410. https://doi.org/10.1371/journal.pbio.3000410

PREPARE: guidelines for planning animal research and testing (Adrian J Smith, R Eddie Clutton, Elliot Lilley et al. Laboratory Animals Volume: 52 issue: 2, page(s): 135-141

OBSERVE: guidelines for the refinement of rodent cancer models. De Vleeschauwer, S.I., van de Ven, M., Oudin, A. et al. Nat Protoc 19, 2571–2596 (2024). https://doi.org/10.1038/s41596-024-00998-w

LASA Guiding Principles

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

We follow the NC3R's website to keep updated on relevant 3Rs initiatives (https://www.nc3rs.org.uk/news/using-award-scheme-promote-3rs-innovation). We actively participate in the animal research (*in vivo*) community, attending and supporting presentations at conferences relevant for oncology tumour models in rodents and in the laboratory and new learnings, refinements, and advances are brought back to the scientists for discussion. We actively discuss new 3Rs initiatives regularly, and implement as appropriate. The council who oversees our animal work also runs a yearly 3Rs competition to facilitate the sharing of 3Rs information globally across different establishments. A large number of our scientists participate in this event to stay informed about new initiatives and seek ways to use them in our research practices. Our team has been recognised with 3Rs awards at this event on multiple occasions. We actively set annual refinement goals, for example, refining mouse handling. Finally, we work closely with the Named Information Officer at our establishment, and this is a valuable source of information on new initiatives and 3Rs, which we then seek to use in our animal research when possible.

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