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NON-TECHNICAL SUMMARY

Pharmacokinetics of novel therapeutic agents and disease modification in oncology

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

Drug discovery, ADME, 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?

The overall aim of this project is to develop novel therapeutic compounds to combat human diseases, including cancer. This involves identification of proteins that are important in causing the disease, understand its chemical structure and function, then designing novel compounds that can control them.

The first aim of this project is to provide animal tissues and cells from freshly-killed animals to test novel compounds in the laboratory, where relevant cell lines for in vitro testing are not available. Each animal can provide sufficient material to test multiple compounds, and this helps reducing the number of subsequent experiments with live animals.

The second aim is to understand how the novel compounds behave and are processed by the body (ADME profiling), which can lead to better design of drug-like compounds. We aim to find compounds that are able to reach the target disease tissue without significant health risks. The most promising compounds are then tested in disease models at Astex (cancer) or externally (cancer and other diseases).

The third aim is to test the activity of the potential anti-cancer compounds in the animal models. The overall effects we desire is the killing of cancer or slowing of its growth. Our investigation also requires studying of key molecular events that are important in cancer cell survival, then the impact of our novel compounds on these events.

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 investigation will lead to identification of novel therapeutic drug candidates which can be tested in human patients. If testing in clinic is successful, these will widen the therapeutic options for patients. Our investigation will lead to further knowledge of the diseases and builds experience of drug-discovery. Early studies, such as the ADME studies, are used to identify the areas of molecules that should be improved. Building data like these improves the efficiency of novel drug designing.

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?

Majority of our studies will use mice. We expect to be using up to 39,300 mice in total during the 5-year period of this licence. We will perform smaller number of experiments with rats, with the total of up to 3,850 animals in the same period.

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?

Majority of the animals will experience mild to moderate adverse effects due to non-surgical intervention (blood sampling, injection, oral dosing), therapeutic drugs, tumour growth or the combination of all.

For the early phase of compound development, each animal will be given injection or oral doses of novel compound at low levels that is not expected to have any therapeutic effects, and blood samples taken to determine the compound level in circulation. These procedures should only cause momentary discomfort immediately after. The therapeutic dose levels and regimen are estimated for the promising compounds and their tolerability tested in pilot experiments. Upon repeat dosing of an anti-cancer compound, we expect that the animals experience mild to moderate side effects such as weight loss, transient diarrhoea and changes in normal behaviour. Since the compounds are novel and despite our effort to predict toxicity risks in vitro, it is impossible to avoid rare events where the animals experience severe adverse effects or die due to toxic effects. We monitor animals on this type of pilot studies daily or more frequently in order to stop suffering as soon as possible. The studies are repeated with lower doses until a tolerated dose schedule is found.

Efficacy of anti-cancer compounds is tested, initially, in subcutaneous xenograft models in which mice are growing human cancer under the skin. In these, each animal receives tumour implantations, which is minimally invasive and can be monitored externally. Any animal, on or off drug treatment, with its tumour approaching a set maximum burden (14 mm in average length in mice, and 25 mm in average length in rats) or appearing to be breaking up will be killed. Therapeutic compounds are administered at the dose that was found to cause adverse effects of moderate levels or less. Treated animals will be monitored to measure efficacy or killed to investigate the drug effects in tumours ex vivo. With most models, some animals (typically 5-20%, depending on the cell line) fail to develop tumours. These may be killed or re-used to investigate the drug exposure and tolerability of novel therapy. Only the most promising compounds may be tested in leukaemia or mammary tumour models which are more invasive and complex than subcutaneous models, and requires extra tumour monitoring methods. Hollow fibre assay offers a means to test multiple cell lines in parallel, where animals receive implantation of multiple fibres containing cells under the skin followed by treatment.

We also aim to improve in vitro screening by using fresh tissues which this programme provides. Animals are humanely killed without any treatment, or receive procedures under general anaesthesia and killed before recovering from anaesthesia. Some animals may receive prior injection of non-therapeutic compound(s) which may cause mild and transient discomfort.

Any animals that suffer adverse effects likely to exceed stated severity will be killed. All animals used in the experiment will be killed on completion of the study.

Replacement

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

We have built multiple ways to test novel compounds, including an extensive list of in vitro biology, ADME and toxicity studies which replaces some of the animal work. Drug properties and efficacy are, however, dependent on the complex system involving multiple organs which cannot be mimicked sufficiently in vitro, so the overall effects of the compounds can only be tested reliably in animals.

For some diseases, cell lines that best represent the target organ and diseases are rare. Primary cells and tissues from limited number of freshly-killed animals can provide materials to test compounds prior to proceeding to in vivo studies. This replaces testing using many live animals.

Reduction

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

We will follow the in vitro compound selection system to avoid testing compounds that are sub-optimal in studies involving large groups of animals.

Where blood collection is needed, we use multiple micro-sampling from each animal, reducing the overall number of animals.

We will re-use animals that failed to develop tumours (typically 5-20% of mice subcutaneously implanted with tumours) in tolerability and ADME studies.

Ex vivo assays reduce overall usage of animals as organs from each animal provides sufficient material to test several compounds.

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.

We will use primarily mouse for screening. Established protocols for testing drugs and historical data are widely available in the literature for this species. Ways of testing treatment effects on human cancers in mice are also well-established, allowing investigation of clinically-relevant disease tissues. We will perform the screening using subcutaneous tumour models as it is the least invasive and causes the least discomfort to the animals.

Rats are another well-characterised species for which many study protocols are established. These are also useful in predicting the drug-like properties and activity of compounds in humans.

Whenever possible, pilot experiments will be performed using the same strain, sex and supplier of mice as those intended for later studies involving disease models to ensure consistency and better prediction. Tolerability of drug treatments may be confirmed in tumour-bearing animals so that we are aware of the combined adverse effects of treatment and tumour development, if any.

Appropriate statistical methods will be used to design experiments and to confirm the finding so that the scientific data reported are reliable.

We consult current and emerging guidelines on animal research and implement improvement in regulated procedure when applicable. These include attempts to reduce stress by sugar-dipping oral dosing needle to make it easier for the animals, and using coloured restrainers. Use of temporary tail vein cannulation may also replace surgical cannulation of animals.