G. NON TECHNICAL SUMMARY (NTS)

Project title: Pharmacokinetics of novel therapeutic agents and disease modification in oncology
Duration of project - years: 5
Duration of project - months: 0

Purpose of the project (as in ASPA Section 5C(3)):
(a) basic research: YES
(b) translational or applied research with one of the following aims:
   (i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants: YES
   (ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants: NO
   (iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes: NO

(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 aims mentioned in paragraph (b): NO
(d) protection of the natural environment in the interests of the health or welfare of man or animals: NO
(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work: NO
(f) higher education or training for the acquisition, maintenance or improvement of vocational skills: NO
(g) forensic inquiries: NO

Keywords:
Drug discovery, ADME, cancer

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):
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
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studying of key molecular events that are important in cancer cell survival, then the impact of our novel compounds on these events.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the 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.

What types and approximate numbers of animals do you expect to use and over what period of time?

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 2,600 animals in the same period.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels 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.

The Home Office, in line with the rest of HM Government, has implemented the Government Security Classification (GSC). Details of the GSC can be found at https://www.gov.uk/government/publications/government-security-classifications. Please note that documents and emails you receive may contain specific handling instructions.

Handling instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location. All government information may be subject to an FOI request and subsequent assessment.
Application of the 3Rs

Replacement:
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:
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:
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.