G. NON-TECHNICAL SUMMARY (NTS)

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed programme of work clearly using non-technical terms which can be understood by a lay reader. You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary will render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at www.gov.uk/research-and-testing-using-animals.

Word limit; 1000 words

Project Title	Radiolabelled molecules for cancer imaging and therapy
Key Words	radioisotope, Cancer, targeted radiotherapy, chemotherapy, imaging
Expected duration of the project	5 year(s) 0 months

Purpose of the project (as in ASPA section 5C(3))

Purpose	
Yes	(a) basic research;
	(b) translational or applied research with one of the following aims:
Yes	(i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants;
No	(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.

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):

This project has 3 parts: 1) Optimisation of a technique (targeted radiotherapy (TR)) delivering radioactive molecules to cancers to destroy them (2) Characterisation of nove lradiolabelled probes that can be used to detect cancer (3) Measure the efficacy of anticancer drug combinations and the effect of treatment on the uptake of radiotracers used in medical imaging.

1) Cancer patients often present with metastatic disease where cancer cells have spread from the primary cancer to establish new cancers elsewhere in the body. Whilst radiotherapy is the most effective anticancer treatment for cancers that cannot be surgically removed it cannot be used to control metastasis. Currently chemotherapy drugs, which distribute around the body, are used to treat metastases but cancers and their metastases almost always develop resistance to chemotherapy. Targeted radiotherapy (TR) involves injecting radioactive drugs targeted to cancer cells which seek out primary tumours and metastases and use their radioactive payload to locally irradiate cancer tissue. In this project we will produce molecules capable of delivering the necessary radiation dose to tumours and their metastases. They will be tested on biological models for efficacy and safety. Results from this study will provide requisite data for a full clinical study.

2) Early cancer detection is critical to long term survival. Positron emission tomography (PET) is the most sensitive medical imaging technique for cancer detection. Currently patients are administered with a radioactive tracer called FDG which is concentrated by cancers facilitating detection of the cancer in the body by the PET camera. Although FDG is very useful its uptake is not restricted to cancer so novel cancer imaging agents are under development. These need to be tested to determine their cancer targeting potential and suitability with respect to where they locate in the body and how long they stay in the body.

3) Combinations of drugs can increase the anticancer effect compared with giving a single drug but cancer response varies between patients. When a cancer is responding to drug treatment, the uptake of a radiotracer by the cancer tends to decrease (this is measured in patients using a PET camera). Here we will test how combination treatments modify the uptake a radioactive tracer to justify using PET in patients to detectresponse to drug combinations.

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)?

1) The anticancer efficiency of targeted radiotherapy (TR) is limited by the poor distribution of the TR molecules within cancers due to regions in cancers where blood flow is poor and due to variation in the amount of TR-target that different cancer cells display. To overcome these problems this project will determine the optimum chemical makeup of the TR molecules. This optimisation will provide the most suitable molecules for a subsequent clinical study. 2) Medical imaging techniques including PET which detects radioactive molecules (tracers) that are attracted to cancers are proving to be very useful in cancer detection and in identifying response to treatment. Novel tracers are being developed which are attracted to cancers but less so to non-cancer tissue to more precisely identify cancers and so reduce uncertainty in cancer diagnosis. 3) Changes in the uptake of tracers during treatment (compared with before treatment) can signal response or non-response at an early time point. Where patients are shown not to be responding to a treatment combination it can be changed to a more effective one.

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

1) Project 1 should take 2-3 years and will use about 250 mice in order to optimise our targeted radiotherapy molecules. 2) Project 2 will be ongoing as new tracers are produced (maximum of 4). Each study will need 50 mice (total of 200). 3) Project 3 will examine treatment efficacy and the effect of treatment on the uptake of the tracer and require 200 mice. This study will take 2-3 years.

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?

Tumours (cancers) will be induced in some mice by subcutaneous (under the skin) injection of cancer cells into the flank. Initial injection may be associated with some inflammation. Tumours will be grown to a maximum size of 15mm (longest dimension) which will not hinder movement nor will they spread as the animals will be humanely killed after a few weeks. This type of procedure is generally assigned a moderate level of severity. Some animals will be injected with clinically relevant doses of radioactive molecules that target the cancers and are not expected to have any adverse effects. Some mice will receive anticancer drugs that target signalling pathways in cells and are not expected to exhibit any side effects (mild level of severity). At the end of each experiment mice will be killed by a humane method and tissues collected.

Application of the 3Rs

Replacement

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

Replacement

1) NC3Rs website has been examined for possible cancer models that could replace animals. A 3D model that is less than 1mm in diameter was found. However we need ones that are 10-15mm in length as we need to demonstrate that the targeted radiotherapy molecules distribute within a solid tumour and produce a uniform dose distribution throughout. The dose is deposited (killing cancer cells) up to 10mm away from the decaying nuclide so the tumours need to be 10-15mm in length to facilitate uptake within a cell kill range. This is in common with comparable studies in the literature. No alternative models for the development of targeted radiotherapy molecules could be found.

2) To determine how a novel imaging agent distributes within the body, how long it stays in the circulation and its excretory route are essential information before a novel cancer imaging agent would be allowed to be used in the imaging of a patient. To determine how the uptake of tracers is influenced by treatment response is initially tested in vitro using isolated cancer cells. However in vivo many other factors influence what happens to the tracer so *in vitro* findings need to be verified *in vivo* prior to clinical translation.

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

1) *In vitro* studies using cells grown in culture can be used to determine the sensitivity of cancer cells to types of cytotoxic radionuclide and to drugs. We will use these methods to inform on the levels of anticancer agents likely to cause tumour regression. Pilot studies based on these findings and the literature for comparable studies will reduce the number of animals required to determine sensitive anticancer agent doses.

2) To ensure that the *in vivo* studies are justified tracers will be screened for specific binding to cancer cells before they are tested *in vivo*.

Refinement

Explain the choice of animals 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.

Refinement

Xenograft (cancers derived from human cancers and grown in animals) cancer models are grown in immunocompromised mice. The mice will be frequently checked to ensure that injections of cancer cells, anticancer drugs, radioactive tracers do not produce any unexpected adverse effects. Formation of a lump within 24h after injection or increased licking of the injection site would give an initial indication of an (unlikely) adverse effect. The animals would be expected to show no adverse effects but would be closely monitored for changes in appearance.

At the end of procedures the animals are humanely killed and tissues analysed

or some of the studies we will require a large blood sample which can most humanely be acquired by cardiac p uncture under terminal anaesthesia.

Where oral gavage is used to administer drugs flexible tubing will be used to decrease the discomfort experienced by the animals.