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	Studies of cancer inflammation and immunity in vivo
Key Words	Immunotherapy, inflammation, tumour immunity, immune-escape, cancer immunology
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;
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.

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

Our main objective is to elucidate which signals trigger anti-tumour immune responses, and to distinguish mediators favouring tumour elimination from those that support cancer progression.

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)?

The recently reported unprecedented efficacy of immunotherapy in a proportion of cancer patients has revolutionised the way we treat cancer. In turn, this has highlighted the need for more mechanistic studies to determine why some patients show partial response or do not respond. In this context, the study of the mediators that regulate the function of immune cells in the tumour microenvironment, distinguishing mediators promoting tumour immunity from those that support tumour growth, is critical to our ability to maximise the efficiency of therapy for cancer patients. The benefits of this project will be: 1) The generation of genetic evidence to show if and how the immune system blocks cancer development in mouse models of cancer that very closely recapitulate the human disease. 2) To inform and advance our ability to identify cancer patients likely to respond and benefit from cancer therapies aimed at harnessing the anti-tumour activities of the immune system. 3) The generation of novel therapies to disrupt immune suppression and enhance the efficacy of conventional and immune-based cancer treatment in patients.

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

Species: mouse Number of mice: 5200 Period of time: 5 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?

Mice may have tumours implanted under the skin or induced by chemical agents. The growth of tumours will be assessed by either imaging with ultrasound or in the case of subcutaneous tumours using callipers. On occasions the tumour cells may be injected into a vein. Some mice will be irradiated to destroy their own immune cells and replaced with specific populations of cells from donor mice. Chemical agents, such as existing cancer therapies, potential new therapies or agents that help measuring specific endpoints may be administered by a variety of routes including orally or by injection. The majority of animals (up to 95%) are not expected to show signs of adverse effects that impact on their general well being apart from the development of tumours. The vast majority of the procedures will result in no more than transient discomfort and no lasting harm. All the mice will be humanely culled at the end point of the experiments.

Application of the 3Rs

Replacement

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

Replacement

The development and function of an inflammatory and immune response involves many different cell types interacting in a dynamic three-dimensional environment. For example, the progression of an immune response within a whole organism involves changes of antigen expression and presentation that evolve with both time and spatial distribution. Similarly, cancer development and spread involves a plethora of interactions between cancer cells and their surrounding cells, governed by multiple signals originating from both their immediate neighbours and from distant tissues. These factors combined with the involvement of multiple host cell-types and the clonal expansion and migration of effector cells mean such research cannot be carried out in tissue culture alone or reproduced in silico and can only be addressed with the use of animals.

The mouse is one of the model organisms that most closely resemble humans. The human and mouse genomes are approximately the same size, and display an equivalent number of genes, which are functionally conserved. Further, mice have genes not represented in other animal model organisms (e.g. *Caenorhabditis elegans*, i.e. nematode worm, and *Drosophila melanogaster* i.e. fruit fly) such as those involved in adaptive immune responses. Mice can be genetically altered, there is extensive literature concerning the topics of our investigation, and our own studies can be enhanced by combination with many complementary models developed by others in the field. Definitively, mouse models are important for placing the findings of in vitro studies or correlative analysis of human samples into an appropriate and meaningful in vivo context. It is the combination of *in vitro* and *in vivo* studies that provides the insight needed to understand cancer biology and develop new therapeutic approaches, and there are no effective approaches to hand that can replace the *in vivo* studies, as these allow the *in vitro* findings to be tested in an appropriate environment.

Reduction

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

Reduction

The use of mice will be minimised in several ways:

By doing as much preliminary work as possible in culture models in vitro and in silico analaysis prior to engaging in in vivo studies.

By minimising variability in results through utilising inbred strains and by housing them under identical conditions to limit variability.

By performing pilot studies using few mice when no information is available in the literature so that the number of mice utilised in experiments is reduced to minimal levels.

By considering on-going statistical estimation of power requirements in each of the studies, using prior results in order to use the minimum number of animals while retaining sufficient numbers for statistical significance.

By incorporating as many test groups as possible within a single controlled experiment, reducing the number of controls required compared to a series of smaller experiments.

By utilising tissues from different sites on one mouse for both treatment and control samples.

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

The use of inbred and fully backcrossed mice not only reduces intragroup experimental variability but also eliminates incompatibility when cell transfers are carried out between various knockout, transgenic and wild-type strains.

The cancer mouse models that we will use very closely recapitulate the human disease and thus allow to understand the molecular and cellular events and steps involved in the activation of tumour immunity and tumour-related inflammation during tumour development and progression.

Where possible, procedures will be undertaken under anaesthesia with the administration of analgaesia to minimise the experience of pain.

We constantly work to improve husbandry and procedures to minimise actual or potential pain, suffering, distress or lasting harm and/or improve animal welfare in situations where the use of animals is unavoidable. Mice will be maintained in individually ventilated cages under barrier environment, to avoid infections.

When considering which route of administration of substances to employ, we will strive to use the least invasive route whilst maintaining direct control of dose. The choice of route to administer a drug or cells will be such as to achieve “best practice”, i.e. to minimise or avoid adverse effects, reduce the number of animals used, and maximise the quality and applicability of substances and cells to achieve the scientific objectives.