G: PROJECT ABSTRACT

NOTE: This abstract will not form any part of the licensed programme of work. However, the Secretary of State considers the project abstract an essential step towards greater openness and expects them to be provided in every case. Use lay terms and avoid confidential material or anything that would identify you or your place of work. This abstract will be placed on the Home Office website at http://scienceandresearch.homeoffice.gov.uk/animal-research/. Examples of other abstracts can be viewed on this site.

NAME OF APPLICANT

DESIGNATED ESTABLISHMENT

PROJECT TITLE (Section 1) (<50 characters including spaces)

Investigating mechanisms of tumorigenesis

KEYWORDS (Insert up to 5 keywords)

Lymphoma, cancer, genetic modification, mice, zebrafish

In no more than 500 words:
- Summarise your project (1-2 sentences)
- Explain why you are doing this project. Describe the scientific unknown(s) or clinical or service need you are addressing. Give a brief scientific background or other explanation of why the work is needed.
- Outline the general project plan.
- State why you have to use animals and cannot use non-animal alternatives. Where appropriate, say how you will use non-animal studies in parallel with the project.
- Explain how you will ensure that you use the minimum number of animals. Indicate approximately how many animals of each species you propose to use.
- Explain why the protocols and the way they are carried out should involve the least suffering.
- Explain why you chose the particular species of animal.
- Give a brief description of the procedures to be applied to the animals used in this project and describe the expected adverse effects.
- Outline in a few sentences how science will advance, or people or animals will benefit from this project.

Investigating mechanisms of tumorigenesis

The development of cancer is regarded as a multi-step process whereby cells acquire multiple mutations, some of which have deleterious effects. Recent research programmes have uncovered the sequence of cancer genomes. These data have detected a variety of mutations in cancer cells but we are yet to explore whether these mutations have any functional significance in the development of tumours. This project will dissect out the importance of some of these very specific genomic defects to specific subsets of cancers.

Cancers often affect the whole body and depend on interactions with the immune system and the surrounding tissues. It is therefore imperative that we mimic this system in our models. The best way to do this, with current technologies, is to produce genetically modified mice which express genes that have been discovered in the cancer cells of patients. First these cancer genes are expressed in cell culture systems to demonstrate that they are able to induce cells to develop into cancer cells. We can then examine how these cells change in response to the cancer gene, but to fully understand the contribution made by other systems within the body, we must confirm the data obtained in the culture systems in our mouse models. Where possible, we will also employ zebrafish in our work in order to reduce the number of mice used. However, use of zebrafish is limited in some scenarios where the techniques required have not been optimised in this species.

Version 1.3
The first step of our project is to express faulty genes in cells in culture to determine if they are able to cause the cultured cells to exhibit properties of cancer cells. If the genes are able to impart survival advantages in vitro we will then demonstrate that they are able to cause cancers in genetically modified mice or zebrafish, i.e. mice which are engineered to carry the faulty gene. These mice/zebrafish can then be fully explored for the activity of the faulty gene in vivo. In particular, we are interested in discovering how necessary these genes are for the continued growth and survival of tumour cells and secondly, if inactivating the faulty gene in cancer cells causes them to die. These data will have immense clinical application as we can then design drugs which specifically target the faulty gene producing ‘designer therapy’ which will by default have less toxic side effects than current treatments.

The mice/zebrafish will be checked daily for signs of tumour growth by qualified animal welfare staff, fully trained in the husbandry and care of genetically modified mice and zebrafish. Any animals which show clinical signs will be carefully examined and monitored and if necessary euthanized. Clinical diagnostic specialists will assist in the analysis of tumours. We will also monitor the development of cancer in some using non-invasive imaging techniques such as fluorescent imaging. In doing so, we will be able to detect growths before they become invasive and hence reduce suffering.

We will use mouse models in this project as this is the least sentient animal which can be employed for the study of tumour development. The immune system of the mouse mimics that of our own and hence provides an excellent in vivo setting for examination of tumours. The genetically modified mice must be bred to obtain complex genetic backgrounds. Some of these mice will therefore be used purely for breeding purposes and genetic engineering. The remaining majority will come from breeding programmes to produce mice which carry the faulty genes and hence will go on to develop tumours for study. The majority of experiments will be performed on tissues isolated from the animals following euthanasia hence minimising animal suffering and advice will be sought from statisticians in order that the least number of animals can be employed. In addition, we will employ zebrafish as a replacement to mice where technically feasible, for example in studies of some cancers for which the analogous zebrafish system has been characterised. This has yet to be carried out for the immune system and therefore in some cases we will continue to use mice.

We anticipate that this research will inform on mechanisms of tumorigenesis as a result of the expression of products of genomic abnormalities in order that we may develop more efficacious, better tolerated treatments which will improve the survival and quality of life of those patients with cancer.