G. NON TECHNICAL SUMMARY (NTS)

Project title: Development of humanised mouse models for study of cancer immunotherapy
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):
YES
(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:
Transplantation, Cancer, Treatment, Immunotherapy, Safety

Describe the aims and objectives of the project (e.g. the scientific unknowns or
scientific/clinical needs being addressed):
Cancer is a leading cause of death in the UK and most developed countries. The aim of this project is
to refine and optimise novel models for the study of cancer cells and their therapy. The study will
specifically investigate the interaction of the immune system with cancer cells and how the immune
system can be manipulated to eradicate cancer cells in a specific and safe manner.

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 data generated by this study is essential for conducting human clinical trials on novel therapeutic
agents for cancer. It is anticipated that this programme of work will validate innovative models for the
study of cancer in the laboratory, which will enable more efficient and patient-specific screening of
anticancer therapies. It is also anticipated that this programme will directly inform optimisation of novel
anti-tumour therapies that can eradicate tumour cells specifically and with improved patient side effects.

What types and approximate numbers of animals do you expect to use and over what period of
time?:
Up to 8,900 mice will be used over a period of 5 years. Up to 775 rats may also be used during this
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?:
The majority (>80%) of the animals are not expected to show signs of adverse effects that impact materially on their general well-being. No more than 20% of animals are expected to show significant clinical signs as a result of the effects of irradiation and restoration of the immune system, surgery or treatment with drugs. Rarely the severity of these signs may be such that the humane end points may be reached. Mice will be killed if they show signs of ill health, such as weight loss, piloerection and hunched posture or inactivity. All animals will be humanely killed at the end of the experiments.

Application of the 3Rs
Replacement:
The definitive examination of the efficacy and safety of anti-cancer drugs requires examination in intact animals, including those with a competent immune system. This is a necessary and pre-requisite 'final' step for the clinical translation of these cancer therapies and cannot be completed without animal experiments. Much of the proposed work is carried in the laboratory and using human tissue only, thus minimising the need for animal experimentation. Importantly, it is anticipated that this work will lead to the refinement and optimisation of laboratory models of cancer which can be ultimately used to replace experimental use of animals.

Reduction:
Only tumour models and therapies that are supported by compelling laboratory experimental data will be investigated using animals. The studies are designed such that many groups of animals will generate valuable data pertaining to tumour biology as well as the efficacy and safety of therapies. Furthermore, some animals serve as controls for more than one experimental group, whereas in other experiments, the same animal can be used as its own control (for example, by being transplanted by two types of cells). Randomisation and blinding will be used to minimise bias and the total number of animals are significantly reduced by addressing all aims using the sophisticated experimental design utilised in this project.

Refinement:
The models used are optimally suited to achieve the aims and objectives of the study. We have refined the protocols and procedures for the generation and maintenance of these mice to maximise the likelihood of the success of the experiments and to minimise stress and harm to animals. The vast majority of the experiments are designed such that the animals only experience minor discomfort, and serious ill health or death is never an expected end-point.