Home Office

NON-TECHNICAL SUMMARY

Generation of novel antibodies with therapeutic potential

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.

Key words

Transgenic mice, Therapeutic antibodies

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

This project will allow us to develop and evaluate novel antibodies (proteins in the bloodstream that fight infections) for use in the treatment of human disease. There is a pressing clinical need to identify new types of treatment for human disease (for example, the development of novel antibiotics) and engineered antibodies have considerable potential for this.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

What are the potential benefits that will derive from this project?

This project will develop engineered antibodies that will be suitable for administration into humans and will not be rejected by the body or cause an adverse reaction. These antibodies could be used to treat a wide variety of human diseases such as cancers and autoimmune disorders including multiple sclerosis, inflammatory bowel disease and arthritis.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

We will use mice to develop the engineered antibodies. This species is the most appropriate as efficient methods exist to allow us to generate mice that carry a genetic alteration (transgenic mice) within the antibody genes. Approximately 4500 mice will be used over 5 years.

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

The mice that carry the engineered antibodies are not expected to experience any adverse affects. The immune system is still fully functional in these mice so they will not be compromised in any way and are not expected to be at any increased risk from infections. The greatest risk of an adverse effect will be during the immunisation protocols to validate the genetic model. While most substances that will be used to immunise the mice are expected to only generate a mild response, similar to that found from a standard vaccination, it is sometimes difficult to predict the biological response. Immunisations will be performed as early in the day as possible so that mice can be monitored during the day. Following an immunisation, mice will be closely monitored and any animal that shows a deviation from normal health will be humanely killed. We may use adjuvants such as FCA but when we do this is only by sc route and in small volumes and if adverse effects are more than minor or transient then the animal will be killed.

The majority of the mice used (2000 mice) will be killed to obtain pre-implantation embryos for genetic

manipulation. The second largest group of mice (1500) represent those that form the breeding colony. Only a sub set of these will be used for immunisations (600, mild). It should be noted that over the duration of the project, the great majority of the mice (95%) will only undergo mild procedures such as breeding, injections, blood sampling from a vein and ear notching. The small minority of mice that have a surgical procedure such as a vasectomy will be given post-operative pain relief as standard.

Replacement

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

We need to use mice as these have an immune system and antibody structure that is similar to humans making them a good model system for these studies.

Unfortunately, there is no cell culture (*in vitro*) system currently available that can be used to generate appropriately modified antibodies with the diversity, specificity and stability properties that using a live animal (*in vivo)* model offers. Antibody production in a live animal is necessary to obtain the most potent and effective antibodies. Currently there is no *in vitro* system that can be used to model the complex nature of the *in vivo* model.

The advantages of antibody generation *in vivo* include achieving a better diversity of antibodies and this also allows quality control checkpoints to ensure the selection and enrichment of cells that produce antibodies with therapeutically desirable properties.

Reduction

Explain how you will assure the use of minimum numbers of animals.

The breeding colony of mice will be maintained as a minimum number by good husbandry, effective colony management and cohort assignment for immunisations. Breeding pairs will be routinely separated once enough offspring have been generated to avoid overbreeding or wastage of animals.

To minimise animal numbers the choice of the immunisation method and co-administration with substances to stimulate the immune response (adjuvants) will be partly based on previous experience, literature searches and in consultation with experts in the field. Small pilot studies on non-genetically altered mice may be performed to identify the most efficient delivery method before conducting larger experiments. Relevant statistical tools (such as power analysis) will be used to design the studies. We have access to statisticians who we will consult when planning the *in vivo* studies to design experiments that use the minimum number of mice compatible with a rigorous statistical analysis. We will use randomisation of mice into each treatment group when testing different immunisation methods and the person doing the data analysis will be unaware of the treatment groups to avoid unconscious biases.

Refinement

Explain the choice of species 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.

Mice are a small and easily handled species with a highly characterised immune system and well-defined biology. Mice are also short lived, have rapid generation times and are easier to look after than other larger animals. The mice are kept in high quality specific pathogen free facilities with access to food, water and environmental enrichments.

I have been successfully using a non-surgical method to transplant embryos into the uterus of females for many years and this represents a considerable refinement as the mice do not have to undergo a surgical procedure.

For some parts of our research we also use a genetically modified mouse that carries a mutation and is sterile and we would like to try using this rather than male mice that have been made sterile by a surgical procedure.

The speed of antibody response in non-genetically altered mice and the optimal routes for delivery of different antigens are very well characterised. For example, good antibody production is found for soluble proteins by injections beneath the skin or into the space surrounding the internal organs. The route of injections used in this project (eg under the skin or into the bloodstream) are expected to cause no or minimal adverse effects whilst inducing effective antibody responses in most cases.

We will minimise harm to the experimental animals and improve their welfare and well being by ensuring acclimatisation before any procedures are performed, accustomise them to being handled, using reduced injection volumes and using a check-list of health observations.

Freund’s complete adjuvant (named after Jules T Freund) is a substance that is mixed with the antigen and can stimulate the immune response. Freund’s complete adjuvant contains inactive mycobacteria and we have found that this gives such an excellent immune response that it only needs to be given once thus reducing the chances of an adverse reaction.

Small pilot studies will be conducted to ensure that the methods used provide for the maximum animal welfare in relation to the study objectives. Pilot studies involve using a small number of mice to test the safety and efficacy of a method before using it on a larger number of mice.