Home Office

NON-TECHNICAL SUMMARY

Mechanisms of Normal and Leukemic Haematopoiesis

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.
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants.

Key words

Haematopoietic stem cells; leukaemia; haematopoiesis.

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?

Our goal is to improve the treatment for children and young adults who suffer from a rapidly fatal type of bone marrow cancer called acute leukaemia. Some children can be cured, but the treatment is arduous – lasting up to 3 years – and medical side effects aside, it severely impacts their schooling and physical development and in some cases impairs normal psychological development. Each member of a family with a child blighted by leukaemia is profoundly affected; parents may have to stop working, and siblings may have life opportunities curtailed. Finally, an emerging problem with current treatments is the prevalence of major long-term medical complications in survivors. It is estimated that dealing with these so-called “late effects” now places as big a burden on the NHS as treating the children in the first place.

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?

Clearly, there is a need to make treatments faster and more focussed so that we can cure all children and minimise the medical, economic and wider societal impacts of leukaemia. We are working towards this by studying the biology of bone marrow cells collected from affected children. We are also looking at ways of improving bone marrow transplantation (an important treatment for patients with leukaemia), and for this we must study normal human blood and bone marrow cells, and cells isolated from human umbilical cord blood. We collaborate with doctors at various hospitals around the country to collect surplus cells that are left over bone marrow tests carried out on patients with leukemia. These tests are painful, and are not undertaken lightly and so the samples are precious. We try to work as much as possible in the tissue culture lab, although some experiments involving mice are inevitable – particularly when we have identified new drugs or treatments which must be tested in mice before clinical studies in children can be contemplated.

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 only use mice in our experiments and a maximum number of 8500 over the 5 years of the experiment. As most mice are ordered for specific experiments wastage will be kept to an absolute minimum.

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?

Our animal experiments involve mice only. We inject human cells into the animals usually through a vein in the tail. In some cases, it is directly into the thigh bone via the knee. To minimise stress and discomfort to the mouse they are given analgesia. 12-24 hours before the human cells are injected, the mice receive low doses of irradiation. Most patients receiving bone marrow transplants receive equivalent doses of radiation, and experience no immediate ill effects However, over the following weeks their immune systems are suppressed and they are prone to infections. To prevent this from happening to our mice we keep them in very clean conditions. Mice receiving normal human cells experience no ill effects. However, those receiving cells from patients with leukaemia can become quite unwell. They are monitored every day by skilled animal technicians, and if there are signs that they are becoming unwell before an experiment is scheduled to finish, they are culled immediately. Whenever this happens the mouse is analysed very carefully, so that we can maximise the information gained from each experiment. Some mice are given chemotherapy or other newly developed drugs. Generally, this is given in the food or water, or by injections either into a vein in the tail or into the abdomen. Occasionally the drugs have to be administered by a feeding tube, and this is carried out by specially trained technicians. Some animals may become unwell after receiving these treatments, and when this happens, they are culled immediately. All animals are eventually humanely culled but, all mice are analysed in detail in our laboratories in order to maximise the data we generate from each experiment.

Replacement

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

We have explored the possibility of experimental methods that do not use animals, and much of our work is carried out in culture with cells acquired from healthy human volunteers or culled mice. In order to replace animals with in vitro models as much as possible, we have developed a method that allows us to keep normal human and leukemic stem cells alive over a period of weeks. This will help us understand the key features of stem cells.

However, one of the main tests of stem cells is that they can live for many months and can produce all types of blood cells, including more stem cells, and at present this can only be tested in animals. Animal studies are also needed to study the impact of chemotherapy, especially to understand why some cells are resistant to treatment and can cause patients to relapse. In addition, when patient leukaemia cells are injected into mice, they are usually able to grow and divide and so the number of cells increases enormously, which does not usually happen under laboratory conditions. These cells can then be harvested and stored long-term, so that these valuable patient samples can be used in many more experiments.

Reduction

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

The majority of mice used in this project licence will be ordered in for specific experiments rather than breeding. Meaning we can ensure the minimum number of mice will be used for most experiments. We will also use statistical tools to design experiments in order to minimise the numbers of animals used.

Where transgenic lines are used efficient breeding strategies are in place. We will replace breeders before their reproductive performance declines and they become un productive and review the breeding continually to make sure we are making the most of the smallest number of animals possible. If we predict that lines or animals are not required for several months we will adjust the numbers of breeders or take advantage of frozen stock when the need arises again.

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.

Stem cells were first identified in mice in the 1950s, and over the years, mice have become the standard model for studying the biology of stem cells and cancer. Indeed, human stem cells were first characterised in mouse models, and the activity of human stem cells is measured in terms of their capacity to transplant in mice. Furthermore, results obtained in mouse models have provided the experimental basis for bringing several new anti-cancer drugs to the clinic.

To ensure technical competence, the staff performing the experiments will be fully trained and supervised either directly by myself or senior postdoctoral fellows who have extensive experience in experiments on animals and the techniques we will be applying.

To minimise infections in immunocompromised mice extra steps will be taken to minimise cross infection from other colonies, like specific protocols for the cleaning and handling the mice. If mice are in pain or discomfort an analgesic will be given. Transgenic mice exhibiting any unexpected harmful phenotype will be humanely culled. Or in the case of any mouse of special scientific interest, advice will be promptly sought from the Home office inspector or Named Veterinary surgeon and the Named Animal Care and Welfare officer. All the work involving mice will be undertaken with the guidelines set out in National Cancer Research Institute (NCRI)