



Home Office

NON-TECHNICAL SUMMARY

Extrinsic regulation of haematopoietic stem and progenitor cells in health, disease and as a therapeutic target

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

blood stem cells, leukaemia, microenvironment

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?

The overall purpose of our project is to understand how blood production is controlled and whether this goes wrong when blood cancers arise. The goal is to improve the production of blood cells and the cells that protect our body from infections (the immune system).

1. Control of blood cells by the nervous system.

Different types of neural cells are found in blood-forming organs, containing blood stem cells, which can give rise to all the different cells that compose our blood and immune system. Other groups and ours have learned that the nervous system regulates the flow of blood cells between the bones and the bloodstream. We have also recently discovered that it might also control the number of blood cells produced.

Questions:

When and how do the neural cells migrate to blood-forming organs? What happens if the neural cell migration is impaired or delayed?

Do neural cells have a specialised function in tissue regeneration?

How do nerve and blood cells interact? Are nerve endings different across different areas of the bone marrow and do these nerves serve different purposes? A subset of nerve fibres can be stimulated by nicotine to investigate the function of these fibres

2. Ageing of the environment where blood is produced.

Increased production of certain blood cell types occurs during normal ageing. This seems to increase the likelihood of developing certain age-related diseases, like blood cancers (such as leukaemia).

Questions:

What are the features of the aged environment where blood stem cells reside?

Can stem cells or other young blood cells rejuvenate the aged blood?

Do nerve cells regulate blood production during ageing?

3. Can we target the environment where blood stem cells reside to improve haematological cancers or abnormal blood production?

We will use mice to simulate models of human blood cancers or diseases producing too many blood cells. Additionally, we and others have found that the environment can protect cancer cells from therapy. Therefore, targeting this environment might help eliminate these cancer cells.

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?

The blood disorders studied represent important clinical needs.

Blood diseases, such as myeloproliferative neoplasms, are chronic diseases with no known cure except for bone marrow transplantation, which is only recommended in a minority of patients. Myeloproliferative neoplasms significantly reduce the quality of life, and are costly given their chronic nature, they also cause other complications like strokes and other bodily haemorrhages. One of the problems we face treating these diseases is that we do not understand all the mechanisms driving manifestation and progression of these diseases. We will try to understand some of these mechanisms through our programme of work. We aim to use our results to devise new therapies for blood disorders.

We also study more acute and aggressive blood cancers such as acute myelogenous leukaemia. In this disease, patients are usually treated with chemotherapy, but evidence indicates that the body actually protects some leukemic cells from chemotherapy. We try to understand why this is the case and try to find some drugs that will target this process and stop leukemic cells from surviving, at the same time as preserving healthy cells.

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?

Approximately 14,100 mice or fewer over the course of five 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 majority of animals (~75%) are expected to show no or mild adverse effects as they will be used in transgenic breedings.

7-14% of the animals in this licence will be used in experiments that involve blood sampling and the administration of compounds that could result in temporary, short-term harm during the procedure. Some of these animals will be treated as above but some genes in their body will be missing to mirror the blood diseases we study. These animals will look normal but will often have clinical signs such as elevated white cells in their blood.

7-9% of the animals in this licence will undergo irradiation to enable transplantation of cells. When this happens, even though we give some helper cells to the animals to help them out just after the irradiations, the animals often lose some weight during the first two weeks but regain it after that. 0.28% of the animals in this licence will undergo transplantation as above and then they will undergo surgery to implant an imaging apparatus that enable us to trace cells in real time. That window will be removed within two hours after implantation. The animals in this paragraph are expected to show moderate signs

of severity such as weight loss.

1.1% of the animals will undergo surgery where peripheral nerves ending in the bone marrow will be stimulated. Of those, 2/3 will not be recovered after anaesthesia so they will not experience any adverse effects. From the 1/3 that will be recovered, some might have trouble walking for the first hours as there will be a sutured incision on them but drugs to minimise pain will be provided and the animals will be sacrificed within 12 hours after recovery.

All animals will be sacrificed by a legal method at the end of the experimental protocols.

Replacement

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

As we are studying the way in which bodily systems interact with one another, it is necessary to use whole animals to determine these factors. Mice have long been used in laboratory studies as the results obtained can often be replicated in larger mammals and eventually humans. It is also not possible to replicate our experiments on small tissue samples as we are unable to measure the larger microenvironment interactions (specifically the input of the nervous system and the blood flow).

When possible, we use alternative methods, like cells cultured *in vitro*. This is where previous cell lines have been preserved and grown outside of a living animal. These can be used to cultivate stem cells and attempt to mimic the microenvironment for short term experiments. However, these eventually need to be transferred to animal research to continue studying the interactive effects in the whole bodily environment.

Reduction

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

In order to reduce the number of animals used, we will try to use as many tissues as possible from each animal and store different samples that can be used for diverse assays. Surplus tissues will also be given to collaborators and other researcher scientists, upon request, to reduce the number of mice needed for research.

The number of animals used in the entire programme of work will be minimised by careful planning and scheduling of breeding and experiments and by using the minimum number of animals to answer the question posed to perform unbiased studies.

As previously stated, we try to isolate specific genes in mice through previously sacrificed mice whose cells have been preserved and given to us by other labs. This helps us identify family or gene groups beforehand and allows us to narrow the breeding and experimental groups needed.

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.

Using mice as a model system has well-established benefits such as: a short breeding time, large litter numbers, short life span, easily genetically modified, and easily translation to human therapeutics.

We use mice as most of the desired genetic modifications have already been established in other labs making ours immediately comparable with the published literature. When using genetically-modified mice, we will try to use models whereby we can control manifestation of disease or harmful phenotypes to reduce the time and grade of such phenotypes, which we will closely monitor. Most of the mice we use are not expected to present any adverse effects and the vast majority of our procedures performed will be minimally invasive and are not expected to produce long-lasting harm.

In our leukaemia experiments, we try to minimise the time that the animal is sick and during that time, we try to reduce the burden of the disease using therapeutic agents, in line with our research questions.

Other experiments require irradiating mice to eliminate some cells and be able to change the blood cell composition. We aim to alleviate any suffering by splitting the irradiation and co-injecting helper cells.

On occasions, we will use treadmill exercise an alternative established and non-invasive model to stimulate the activity of the nervous (avoiding the requirement of drugs).

In the rare case of invasive procedures with a larger impact, such as terminal bleeds and a subset of surgeries, the animals are anaesthetised prior to the procedure but not recovered after that, so that they will not experience any pain.