NON-TECHNICAL SUMMARY

Investigation of the genetic drivers and therapeutic vulnerabilities of myeloid leukaemia and related cancers

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.
  - (iii) Improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.

Key words

Leukaemia, Ageing, Mutation, Treatment, Blood disorders

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?

Acute myeloid leukaemia (AML) is an aggressive cancer of the blood that rapidly leads to death if untreated. If AML is treated in time with intensive chemotherapy, this can lead to complete remission of the cancer (i.e. clinical control of the disease). However, in most cases the AML returns in a more aggressive form leading to the death of most patients, although some can be rescued by bone marrow transplantation. Overall less than 30% of AML patients survive long-term, a statistic that has improved only very modestly over the last 20 years, highlighting an urgent unmet clinical need. Additionally, other cancers related to AML, including the myelodysplastic syndromes (MDS) and the myeloproliferative disorders (MPD) whilst less aggressive, also remain incurable and lead to the demise of most sufferers. Also, these diseases are much commoner in older people for whom intensive chemotherapy is inappropriate.

The reason for this lack of progress has been our poor understanding of how AML and related cancers develop and what their treatment vulnerabilities are. Over the last few years, the development of DNA sequencing techniques has enabled us to identify the genetic changes that drive AML, understand how they disease develops and help us develop new treatments.

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 proposed project aims to directly address an unmet clinical need and help develop new treatments against AML and related cancers by: i) improving the understanding of how genetic changes cause AML, ii) understand the role of ageing in the development of these diseases and iii) identify potential therapies.

It is hoped that the proposed work will identify and validate new treatment targets against AML and related cancers. Our aspiration is to help develop new treatments that can be tested in patients within the next decade. Also, we hope to identify factors related to ageing that affect leukaemia development in order to prevent the disease from developing.

Findings will be made available to other scientists through publication in open access, peer-reviewed journals or on open access platforms, and presentations at scientific conferences and meetings. The transgenic animals developed will be valuable to other scientists interested in the study of leukaemia and other cancers.

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 plan to use up to 27,000 mice, most of which will be used for breeding. Animals used for experiments will be: i) mice with genetic changes to introduce and study human leukaemia mutations, ii) mice aged to investigate the impact of ageing on leukaemia development, and iii) mice used to identify or test the validity of new treatment approaches.

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?

Mice will be kept in individually ventilated cages with a maximum of 5 mice per cage with food and water always available. Genetically modified (GM) mice with human leukaemia-causing mutations will be kept for up to 20 weeks and then killed to obtain cells for study. Others will be kept for longer to determine if they develop leukaemia. Some will be given injections, including into the thigh bone cavity and under anaesthesia, to give them mutated or cancerous/pre-cancerous cells or to activate mutations. Injections into the thigh bone cavity are needed because certain types of leukaemia do not grow if injected elsewhere. Some mice will receive prior irradiation to enable injected cells to grow and not be rejected by the immune system. Some GM mice will be aged to test if they develop leukaemia and some will undergo non-invasive imaging to quantify leukaemic cell numbers/volume. Mice will be monitored daily when at risk, so they are detected early and killed humanely when unwell.

Mice used for ageing studies can develop the normal effects of getting older (e.g. reduced mobility, weight gain, reduced activity), but if they exhibit any signs of more than mild suffering they will be killed humanely.

Mice used to study drugs and therapeutic interventions, will either be those developing leukaemia naturally or others injected with leukaemia cells. These mice will be given treatments used in mice before aimed to reduce, slow or stop leukaemia development. Treatments used here will be given at doses expected to cause only mild to moderate side-effects. However, if significant side-effects are observed, mice will be killed humanely.

At the end of procedures or ageing studies, all mice will be killed humanely.

Replacement

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

Most of our research does not use animals and relies on studying primary human samples and leukaemia cells in culture. However, we need to use mice to study the effects of leukaemia-causing gene changes in the body and appreciate how leukaemia develops in a living animal in order to understand how to reverse this process. Also, animals are required to study how getting old affects
disease and to determine if particular treatments are not only effective for killing cancer cells in culture, but also do the same in a living animal, which is an essential step for progressing treatments towards clinical development.

**Reduction**

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

To reduce the numbers of animals we use we have adapted the breeding strategies to set up matings generating mostly animals with the genetic make-up of interest. Additionally, we draw on our expertise to calculate the minimum number of animals required for our experiments. Also, we recently developed a genome-editing technique for generating blood stem cells with leukaemia-causing changes, which can be transplanted and studied in mice, significantly reducing the number of mice required for creating genetically altered mice.

Experiments will be conducted to enable publication of results in open access scientific journals and in accordance with the NC3Rs' ARRIVE guidelines.

Sequencing or genotyping data will be archived at EMBL-EBI’s European Nucleotide Archive (ENA) which is openly accessible to any researcher around the world so that some experiments using animals do not have to be repeated.

Any new animal models we create will be archived in international repositories and made available to other researchers around the world. This will help reduce the number of animals used to make these models by other scientists.

**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.**

To reduce the suffering of our mice, we will be: 1) designing genotyping (DNA) tests so that they can be performed from ear punch biopsies, removing the need for tail biopsies which cause more pain, 2) increasing expertise for better assessment of the welfare of animals at risk of developing tumours/leukaemias so that ill mice are identified early, 3) having a process whereby sick animals are identified as quickly as possible and culled if necessary, 4) developing or importing mice that can be used in transplantation experiments without the need for irradiation, 5) using a mouse strain that enables the transplantation of genetically changed into mice to avoid the need to develop/breed new mouse strains with the genetic alterations, 6) allocating technically difficult procedures to the best-trained team members to ensure they maintain their skills and minimise operator issues with procedures.

**Surgery**
Mice will be kept warm following surgery to ensure they remain warm.

**Analgesia**

All animals may experience some post-operative pain or discomfort following surgery. Pre-, peri- (during) and post-operative pain killers will be given and maintained after surgery for as long as is necessary to alleviate pain.

**Group housing**

Animals will be kept in socially compatible groups.

**Enrichment**

Mice will be kept in deep bedding and will be provided with nesting materials and ‘fun tunnels’.

We use a sophisticated animal tracking system to ensure welfare data on all animals can be readily accessed/analysed.

We will comply with [best practice guidelines, e.g., the Home Office Minimum Standards for Aseptic Surgery and the LASA Guiding Principles for Preparing for and Undertaking Aseptic Surgery, and Guidelines for the Welfare and Use of Animals in Cancer Research (British Journal of Cancer (2010) 102, 1555-77).]