Home Office

NON-TECHNICAL SUMMARY

Mechanism of stem cell homeostasis, cancer and tissue regeneration

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

Stem cells, cancer, regeneration

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 human body is made up of trillions of cells that together form various organs to carry out their unique functions. The growth and maintenance of each organ is supported by the stem cells in the resident tissues, which will respond to damage for tissue regeneration. This is achieved by delicate control of signals given to the stem cells for their fate decision (expand, mature, dormant or die). Dysfunction of these regulations can lead to uncontrolled expansion (cancer) or catastrophic loss (organ failure) of stem cells.

The purpose of this project is to understand how fate decision is controlled by specific genes and genetic pathways in both normal (healthy) and abnormal (trauma, inflammation, cancer and aging) situations. These genetic controls of stem cells are often similar in different organs/systems. The main system we use is the gut, which is one of the fastest regenerating tissues. The sheet of cells covering the entire gut lumen, which is approximately the size of a tennis court, continuously regenerate every 4-5 days. The high turnover rate and the unique architecture of the gut makes it an ideal model for stem cell study.

Stem cell fate decision, tissue repair and cancer are closely linked, while the underlying molecular control is not fully characterised. Our aim is to identify the key genes and their related signalling pathways involved in the stem cell control of normal and cancerous tissues, with the emphasis of finding new drug targets to improve cancer treatment.

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?

Our project is likely to advance the basic understanding of how human body works by stem cell fate decision, to benefit diagnosis of genetic diseases, to inform clinical treatment, and ultimately to improve cancer treatment by providing options of targeted (personalised) therapy.

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?

Around 33000 mice 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 vast majority of our regulated experiments are of the mildest severity and concern the breeding and observation of genetically altered mice and/or minimally invasive procedures such as administration of substances by injection. Adverse effects are neither expected nor seen in all but a very few of these cases. In some cases, the animals will develop tumours, which can be associated with weight loss, signs of discomfort and slowing down of the normal activity. However, the procedures will never exceed the moderate severity level. Any animal approaching severity limits will be killed (Schedule 1), and all animals subject to a procedure will eventually be killed (Schedule 1) and tissues will be used for analysis.

Replacement

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

Cell fate decisions in the animal or an organ take place within a complex environment, where events intrinsic to the cells are influenced by a variety of extrinsic signals. The latter can involve molecules that can act locally or over considerable distances (such as growth factors and hormones), and which may originate from neighbouring cells, or from anywhere within the body (or even be from the external environment such as microbes in the gut). Moreover, most tissues develop in a complex way in three dimensions over time in a carefully orchestrated manner, and require blood vessels and nerves to operate. Therefore, although some aspects of certain cell fate decisions can be studied in vitro, and we both use and develop such approaches, it is generally essential to study them in animals (as a minimum to judge the suitability of in vitro systems to give meaningful information). This is particularly true of the complex systems and processes we investigate.

Reduction

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

Our experiments are designed to use the minimum number of animals required to give robust answers with the use of statistical methods.

We test methods and reagents in vitro whenever possible prior to their use in animals.

We always confirm the importance of the genes of interest in “organoid culture” (3D stem cell culture that consists of organ-specific cell type) in vitro before testing them in animals.

We use efficient method to generate and maintain genetically altered animals, and make use of sperm and embryo freezing to avoid keeping the strains as live animals when a particular study is finished.

We will make optimal use of several tissues, fluid and cell types per individual mouse and will provide the other affected tissues to appropriate scientists so that they do not have to breed mice specifically for their experiments.

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 have been selected for the majority of this work as it is an appropriate model for providing insights into human diseases and it is the species in which reliable transgenic and knockout technologies are most advanced.

We choose well-established protocols known to have minimal harmful effects whenever possible.

To minimise stress during breeding and maintenance, we will follow best practice guidelines and follow local refinements of husbandry.

Whenever practical, we prefer to make genetic alterations that are inducible, so that the animals do not show a phenotype until expression of the candidate gene or a deletion is induced.

For manipulations, we will adhere to local and national guidelines that aim to minimise suffering. If insufficient information is available, new manipulations will be pre-screened in small-scale pilot studies to obtain indications of the minimal dose and exposure time that is likely to be effectively, thereby minimising any potential suffering.

In all surgery, analgesia will be provided according to contemporary best practice and advice from the NVS/NACWO. Good aseptic surgical techniques, heat and fluid therapy will be provided as necessary.