



Home Office

NON-TECHNICAL SUMMARY

Understanding how neutrophil migration behaviour is fine-tuned during inflammation

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

No answer provided

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?

Inflammation is a natural response of your body to injury or harmful agents that permits rapid defence against infection. All of us experience the bothersome symptoms of inflammation at some point or another, which include local redness, swelling and pain. The redness and swelling are in fact associated with the increase of blood flow and the infiltration of white blood cells, which are crucial for fighting harmful bacteria that exploit the opportunity to enter your body upon injury.

A key type of cell that infiltrates inflammatory sites is the neutrophil. It is believed that by controlling the infiltration of neutrophils in tissues it should be possible to increase or decrease inflammation on demand. Why would we want to control inflammation? Excess inflammation is associated with numerous debilitating diseases such as rheumatoid arthritis or chronic obstructive pulmonary disease. Conversely, increasing neutrophil infiltration can be beneficial in some cases of cancer. Current anti-inflammatory drugs have side effects due to their broad mechanism of action. Drugs that specifically target neutrophil infiltration are considered a promising alternative. However, such strategies require careful approaches to manipulate neutrophil migration to balance the trade-off between undesirable excess inflammation and insufficient immunological defence. The overarching aim of this licence is to gain a better understanding of how neutrophil behaviour at inflammatory sites is controlled.

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 work would improve our basic understanding of how immune cells sense and respond to damage and how they move and accumulate in tissues. Work from this licence is likely to unravel new ways to manipulate the behaviour of these cells and inflammatory responses therapeutically. Given the pervasive roles of inflammation in disease and the unmet need to fine-tune this process pharmacologically, the long-term benefit of our work is thus considerable. Examples include chronic inflammatory diseases (such as rheumatoid arthritis, asthma or chronic obstructive pulmonary disease) or cancer (such as pancreatic cancer, which has been linked to neutrophil migration and remains one of the most incurable cancers). Our work will also generate new, non-mammalian animal models that could partly or largely replace mouse models for the purpose of drug discovery research.

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?

12525 adult zebrafish 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?

There are no specific adverse effects expected in relation to breeding the animals or the genetic modifications used. In limited cases (up to 5%) we will need to anaesthetise fish to collect eggs and sperm for In Vitro Fertilisation (IVF) or for verifying the genetic status of the animals (up to 40%). The latter entails either observing the fish for manifestation of the genetic alteration or direct assessment of DNA from small tissue biopsies, causing minimal temporary discomfort. Our procedure will be carefully monitored and continuously refined to eliminate or minimise any pain or suffering. In the unlikely event that something unexpected occurs, affected animals will be immediately killed. Fish produced under the authority of this project will either be used on this licence or excess stock will be supplied to other projects with authority to use genetically altered fish of this type.

Replacement

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

The key aspect of our programme is to visualise neutrophil behaviours in situ by advanced microscopy techniques, to discover new mechanisms regulating this process. This is because the cell behaviours we study are difficult to recapitulate outside the body. We propose to use the zebrafish larva, under 5 days post fertilisation, which is a much simpler organism, not capable of independent feeding and complex cognitive functions but complex enough to recapitulate the neutrophil behaviours in question. Zebrafish larvae are least likely to feel pain and experience distress as they are at an immature life stage. This represents the simplest organism in which we can perform such studies because invertebrates (e.g. fly or worm, which are typical invertebrate models) lack neutrophils. The zebrafish larva is transparent, allowing non-invasive visualisation of neutrophil behaviour by microscopy (the equivalent process in mammals requires surgical exposure of tissues). Genetic modification is also simpler and less invasive than in mammals. Thus, working with this relatively simple organism entails less invasive methodologies.

Reduction

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

We intend to perform manipulations only on embryos/larvae younger than 5 days post fertilisation (not protected under The Animals (Scientific Procedures Act) 1986. Adult animals (wild type or genetically altered) will be used only for breeding purposes. The limiting factor in the number of animals used is their breeding performance. The quality of breeding activity is continuously monitored and optimised in our facility (for example through keeping a record of breedings, avoiding repeated use of breeders in small time intervals and performing regular outcrosses). This ensures that we don't over-breed fish. To ensure minimal numbers of fish bred we will carefully consider experimental design to have enough animals to answer a scientific question but not more than necessary.

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.

We are always looking for ways to refine our breeding protocols and keep what we do constantly under review. One way we achieve this is through our Zebrafish User meetings, where users, animal welfare experts and veterinarians meet to discuss and exchange good practice ideas. In this meeting, users of the shared zebrafish facility report issues on survival or breeding rates and we discuss and implement better ways of breeding the fish in a consensus manner. A key regulated procedure as part of breeding genetically modified animals is the required verification and screening of zebrafish for the genetic modification. This entails either observing the fish for manifestation of the genetic alteration or direct assessment of DNA from small tissue biopsies. The former will be the preferred method. We are currently testing environmental enrichment as a potential improvement in our practices.