Home Office

NON-TECHNICAL SUMMARY

Understanding gene – environment interaction in inflammatory bowel disease

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

Inflammatory bowel disease, Crohn's disease, arthritis, Infection, Tumours

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?

Crohn's disease and ulcerative colitis are the two major forms of inflammatory bowel disease. These are chronic, debilitating diseases that usually occur early in life and lead to severe inflammation of the intestinal tract. These diseases ruin lives, and can also lead to cancer. The UK is amongst the countries with the highest risk for this disease, it is estimated that ~1 in 200 individuals is affected. Risk for these diseases runs in families, and the genes responsible for this risk have been largely discovered over the last decade. However, the genes in themselves do not cause disease, but it requires other – yet unknown – factors that trigger disease. Unfortunately, even the function of most of the risk genes and how they would lead to disease, remain mostly unknown. Here we aim to study the function of important risk genes to discover the 'pathways' and cells in the body that are engaged that lead to disease. We will also aim to use this knowledge to identify and study environmental factors that may trigger disease in an individual who carries 'risk genes'. In our intestine, we carry an enormous number of bacteria and other microbes, and they seem to be the target, but possibly also a trigger, of a misguided immune response that is typical of inflammatory bowel disease. We will hence study the role of the microbiota and how this affects the triggering of disease.

In summary, we want to understand how IBD risk genes function, and how they interact with environmental triggers. This will not only increase our understanding of the mechanisms that cause disease, but may identify novel targets for treatment that could subsequently be developed into new medicines.

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?

We hope that our investigations will identify new treatment targets for inflammatory bowel disease, and possibly also for other immune-mediated diseases. We hope to begin to understand what triggers may set off intestinal inflammation. This is very important as this disease has become way more common in the Western World over the last decades, and is now also picking up speed in other parts of the world such as Asia.

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?

Over 5 years, we will study ~24000 mice. This amounts to 1.3 mouse per day per researcher.

We have a strong track record of major discoveries in this field over > 15 years, all on the background of adhering to best practice and highest ethical standards. This includes experimental design principles where we apply highest standards including random allocation to experimental groups, and blinded analysis – all meant to avoid bias introduced by investigators.

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 genetically-altered mouse lines we study develop entirely normally. They will typically undergo a tissue biopsy from the ear to determine their genotype, and for a large number of animals this will be the only intervention and no adverse effects are expected from that. Mice may be fed specific diets (e.g. high-fat diets), or they may receive antibiotics to modulate the bacterial flora in their intestine – interventions that are typically well tolerated and only few adverse effects would be expected that we will monitor for (e.g. diarrhoea).
In a small proportion of mice we will induce colitis, infection, arthritis, or tumours. This can be associated with diarrhoea, weight loss, and compromised overall well-being. No more than 10% of animals studied in this project license are expected to show moderate clinical signs such as piloerection. Very rarely the severity of these signs may be such that the humane end points may be reached. Animals are monitored on a regular basis to detect any sign of distress or suffering. Analgesic agents will be administered as required. In the event of complications, or at the end of the experiment, animals will be killed by a schedule 1 method.

Replacement

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

The number of mice for this project may seem relatively high, although it is ~1.4 mouse per day per researcher. This is due to the lack of reliable in vitro models that capture the complexity of the intestinal tract: there is a myriad of microbes in faeces, and a thin layer of mucus and cells that separates them from the body's intestinal cells – which, for example, contain the body's largest accumulation of immune cells. A pathologic immune response to these microbes is a hallmark of inflammatory bowel disease. There are absolutely no *in vitro* models available that would even remotely capture the complexity of the organ and therefore we have to rely on mouse models.

Reduction

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

We are using a wide array of sophisticated *in vitro* experiments, including various types of cells and cell lines, and all sorts of molecular techniques to predict the establish biological mechanisms. This allows us to make predictions and to prioritise those mechanisms that need to be studied in mice *in vivo*.

When designing experiments, we perform statistical analysis to determine the minimum number of mice that are required to perform an informative experiment. We also always aim to maximise the information we can gather from every single mouse.

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.

Animals are housed according to the best recommendations in an appropriate and enriched environment. By performing pilot studies and choosing well-established protocols based on extensive previous experience, we minimise the unknown effects on the mice and hence pain, distress and suffering. We very frequently monitor animal behaviour and well-being to detect any upcoming problem at an early stage.

For one of the most important genetic risk factor of inflammatory bowel disease (which is carried by ~two thirds of all patients), over the last years we have developed a model of small intestinal inflammation that spontaneously develops, and which is not associated with any clinical disease or suffering of the animal. It is purely visible under the microscope. This is a major advance, and we have validated that this closely resembles human Crohn’s disease.