Home Office

NON-TECHNICAL SUMMARY

Understanding pathogen behaviour in relation to the immunity, vaccines and antibiotic treatment

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

Bacteria, infection, vaccine, antibiotic

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 aim of our research is to understand how infections caused by bacteria can be defeated or prevented by making better vaccines and antibiotics. Bacterial infections are a big problem because they cause about 6 million deaths in the whole world. Many bacteria are becoming resistant to antibiotics and many of the vaccines that we use are not sufficiently good. Therefore we do not have optimal weapons to fight infections. We primarily work on bacterial diseases that affect and kill children in poor areas of the world. For example, one of these diseases, invasive non-typhoidal salmonelloses (iNTS) causes about 680,000 deaths every year, 68% of which are in children less than 5 years old in Africa and South East Asia. *Streptococcus pneumoniae*and *Neisseria meningitidis*also cause very severe infections in children and immune-compromised adults worldwide. Currently there are no vaccines against iNTS and an increasing number of iNTS bacteria are becoming resistant to the antibiotics that doctors use to fight them. Better and more affordable vaccines against *Streptococcus pneumoniae*and *Neisseria meningitidis*are also a priority. Furthermore, we do not understand how these bacteria spread in the environment and how they infect people. Therefore better vaccines and antibiotics remain the main weapons to fight these infections in poor countries.

Our research will study how and where the bacteria hide in the body to resist to vaccines and antibiotics and will test new innovative vaccines. . This will enable us to produce new vaccines and antibiotics that can reach the bacteria in the locations where they hide and persist and kill them more efficiently.

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 work will create scientific knowledge that will guide a better use of the vaccines and antibiotics that are currently available to us and will make it easier to produce new and better antibiotics and vaccines. Doctors and patients will benefit from this research that will improve the treatment of sick people, especially children and will also reduce the spread of diseases in the community. These benefits will be stronger especially in developing countries where there are many conditions that weaken the immune system especially in young children (for example, viral infections, gut parasites, malaria, malnutrition). In fact a weak immune system makes vaccination and treatment of an infection a lot harder to accomplish. In the long term, better use of antibiotics and vaccines will reduce the disease burden and slow down or stop the emergence of bacteria that are resistant to antibiotics. Our work will also impact on disease prevention in the veterinary field and in food-animals where vaccines and antimicrobials are widely used often with suboptimal results.

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 13000 mice over 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 animals will be infected with live bacteria via several possible parenteral routes, intranasally or via oral gavage and then may be treated with antibiotics or molecules that affect the immune system. In some experiments, new vaccines will be tested, selected and optimized by immunisation schedules followed by reinfection with pathogenic bacteria and monitoring of the immune responses.
In the majority (> 90%) of experiments no animals will show signs of infection. However, it is possible that very occasionally a small number of animal show clinical signs. These animals will be closely monitored and assisted via careful and skilful husbandry that is typical of the culture of care present at our establishment. If signs persisted for more than a few hours the animals would be killed to avoid further suffering.

Replacement

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

We perform many preliminary experiments in systems that do not involve animals. However, these systems cannot reproduce the complexity of the body of a whole animal where the blood transports the bacteria between different sites and each organ influences the functioning of other organs. Therefore to ensure that our research has a real future impact on human health, it is necessary also to study infections in a whole animal where we can capture the impact of medical treatments and new vaccines on the behaviour of bacteria in an environment that closely resembles the human body.

Reduction

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

We greatly strive to reduce the numbers of animals that we use in our experiments. Whenever possible we perform preliminary studies in systems that do not require animal experimentation so that we can improve our protocols and use smaller numbers of animals only for the final validation of our results. We combine several experiments in one so that, for example, we can compare the effect different vaccines or treatments using just one untreated (control) experimental group. We use the smallest possible experimental number of animals for each experiment being very careful that this does not affect the accuracy of our results. To determine the smallest number of animals that we can use in our work we use calculations bases on advanced statistics and mathematics. Statisticians and mathematicians have become an important part of our research group.

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 use infections in adult mice. This model captures the essential traits of many bacterial infections of humans and other animals. Mouse models are a reliable tool to study vaccines and antibiotics before these are used in humans and domestic animals. The availability of genetically altered mice allows us to mimic model human conditions and immune-deficiencies such as malaria, AIDS, congenital absence of components of the immune system that predispose to infection. The model therefore enables refined studies on the interaction between bacteria and the immune system in the course of vaccination or medical treatments.

Most animals do not show any signs of infection during our experiments. We minimise suffering via careful and skilful handling of the animals, use of the smallest possible size of needles, minimal numbers and frequency of repeated procedures and light anaesthesia for some procedures. Whenever possible we use less infectious bacterial strains for our studies to minimize the signs of infection that may occur. We progressively refine our protocols to ensure that the smallest possible doses of bacteria are administered to the animals and we perform observations at time points before the occurrence of signs of infection. To achieve this we are making use of new technology to increase the sensitivity of our assays that detect bacteria, bacterial genes/proteins, or immune parameters triggered by low numbers of bacteria in the body of the infected animal. This has also the scientific advantage of looking at infections when bacterial numbers are relatively low and more closely related to what happens in the human infections that we model.