G. NON-TECHNICAL SUMMARY (NTS)

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed programme of work clearly using non-technical terms which can be understood by a lay reader. You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary will render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at www.gov.uk/research-and-testing-using-animals.

Word limit: 1000 words

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Understanding pathogen behaviour in relation to the immunity, vaccines and antibiotic treatment</th>
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<tbody>
<tr>
<td>Key Words</td>
<td>Bacteria, infection, vaccine, antibiotic</td>
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<tr>
<td>Expected duration of the project</td>
<td>5 year(s) 0 months</td>
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Purpose of the project (as in ASPA section 5C(3))

Purpose

Yes  (a) basic research;

(b) translational or applied research with one of the following aims:

Yes  (i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants;

No  (ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants;

No  (iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.

No  (c) development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the aims mentioned in paragraph (b);

No  (d) protection of the natural environment in the interests of the health or welfare of man or animals;
(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work;

(f) higher education or training for the acquisition, maintenance or improvement of vocational skills;

(g) forensic inquiries.

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):

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. 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. 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. 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.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the 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.
What types and approximate numbers of animals do you expect to use and over what period of time?

Approximately 10000 mice over five years

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels 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.

Application of the 3Rs

Replacement

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

Replacement

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 ensure the use of minimum numbers of animals

Reduction

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 animals 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.

Refinement

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.