

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

Project Title	Maintenance of barrier immunity in health and disease
Key Words	Lung, Inflammation, Chronic disease, Treatment
Expected duration of the project	5 year(s) 0 months

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;

Yes (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;
No	(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work;
No	(f) higher education or training for the acquisition, maintenance or improvement of vocational skills;
No	(g) forensic inquiries.

Describe the aims and objectives of the project:

Treatments for lung conditions such as infection and asthma have not changed since the discovery of antibiotics and steroids. Huge numbers of patients with lung disease do not respond to these treatments. An alternative approach to combatting inflammatory disease is to identify why healthy people are not inflamed. This approach has led to the discovery of pathways present in health that were absent in disease, which are now of interest to the pharmaceutical industry. This project license continues to develop these ideas, but also begin the next logical strand of research, which is to understand how lung disease causes effects elsewhere in the body.

For example, it is important to understand why some patients with cancer develop secondary cancers in the lung when others do not. Also why do some patients with lung disease develop complications in the skin or kidney? These secondary effects of lung disease cause significant disease and disability in their own right.

What are the potential benefits likely to derive from this project?

More often than not, severe disease and death is not associated with the first inflammatory event, but with subsequent consequences. For example: 1) Patients with severe asthma only get worse disease after bacterial infection 2) Some patients with pandemic flu do not die of flu, but the bacterial pneumonia that follows. 3) Some patients with breast cancer develop secondary lung cancer, which kills them, whereas others do not. 4) Kidney and skin inflammation following lung inflammation occur in some, but not others. Understanding secondary complications, provides an alternative strategy to treat those most severely affected by inflammation.

What types and approximate numbers of animals do you expect to use and over what period of time?

This project licence merges the interests of a number of groups interested in lung, skin, kidney and gut that encompass approximately 15 researchers for 5 years. The maximum number of mice we will breed is 10,000. We will use a maximum of 17,000 mice, which represents approximately 226 per year per person. This relatively low number reflects that the work has now predominantly moved into human tissues.

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?

This project license has an overall severity limit of moderate. To induce lung inflammation, mice are given an inhaled anaesthetic. The agent causing inflammation is then placed as a droplet on their nose, which they also breathe in. They recover from this within 2 minutes. We have many years' experience of the lung inflammation models such that we know how to only induce a moderate illness score. In many cases this represents a bad cold, but on occasions mice may experience influenza like symptoms. No adverse events are expected. The impact of lung inflammation on the spread of distant cancers is only concerned at the earliest stages of lung cancer. At the end of the experiment mice are euthanised using an injected anaesthetic

Application of the 3Rs

Replacement

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

Replacement

At least 60 percent of the laboratories research has now transferred into specimens from patients. This was largely facilitated by relocation to [REDACTED] clinicians [REDACTED]. Acquisition of lung pieces from the surgical team is no possible. Unlike cell lines, this tissue provides relevant cells in their relevant architecture.

Unfortunately, this tissue does not represent all lung diseases and so modelling certain scenarios in a 3 dimensional environment is required.

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

Animal reduction will be facilitated by group members sharing tissue. Rigorous experiment design principles will be employed in the conduct of all experiments, including bias avoidance strategies.

The sample size for decision making studies will be selected based on an understanding of a biologically meaningful effect and the variability in the primary endpoint. See appendix for exemplar group size calculation. Scientific expertise and previous experimental data will be used to assess both aspects. Formal power calculations will be used based on a statistical power of 80% and a significance level of 5%. Where no previous information is available, pilot experiments will be conducted to build confidence in the suitability of the final design. Where appropriate, projects will be designed in consultation with statisticians (Inferstats).

Where an experimental type is run repeatedly (e.g. infection protocol 2), assay performance over time will be carefully monitored to ensure that it is continuing to perform well.

The laboratory has a biobank of specimens from previous experiments that can be used by subsequent researchers. Unfortunately storage processes can alter the expression of some receptors and their ligands and so paraffin-embedded tissue blocks or frozen tissue are only used for the extraction of genetic material. However, these provide an important source for the generation of proof of principle without the need to sacrifice further animals.

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

The use of mice is imperative to the success of this project. The mammalian immune system is complex with many different cells and molecules working in combination within a tissue specific structure. Thus, the use of lower organisms such as Drosophila or zebrafish is not feasible (these organisms do not possess as complex immune systems). In the models we use the symptoms are no more than moderate and mice are carefully monitored for weight loss, condition (piloerection, mobility) and signs of distress (hunched posture, facial grimace). We pay particular attention to training as inefficient processes can lead to distress of the animal and the research scientist. All researchers must treat mice with empathy and respect. To ensure compliance with techniques, no researcher works alone. Animals are handled for the minimum amount of time, in determining the route of immunisation, distress to the animal is considered and i.p is avoided where possible, the needles used are the smallest possible for that procedure and experiments are performed in the minimum time possible.