Home Office

NON-TECHNICAL SUMMARY

Respiratory research to support the development of treatments for lung diseases

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

asthma, COPD, exacerbation, lung disease, respiratory disease

Animal types	Life stages
Mice	Adult, Aged animal
Rats	Adult, Aged animal

Retrospective assessment

> The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

To support the discovery and development of new medicines for lung diseases

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.

Why is it important to undertake this work?

Diseases of the respiratory system, such as asthma and chronic obstructive pulmonary disease (COPD), remain a significant cause of morbidity and mortality across the world. The World Health Organisation (WHO) estimates that 235 million children suffer from asthma and 6% of all deaths are caused by COPD, which indicates there is still a significant unmet clinical need. Understanding the mechanisms which result in respiratory disease enables us to design and develop new medicines which can increase the quality of life for patients and reduce deaths caused from these diseases.

What outputs do you think you will see at the end of this project?

The ultimate goal of this licence is to support the discovery and development of new medicines for human respiratory diseases, and the main outputs will be information about the activity of our treatments in animal models. This information is used together with other results of many other experiments, using cells or human tissues, to understand which potential new treatments to progress into further research. The overall drug discovery process is much longer than the lifetime of a project licence, often taking 10-15 years from the early research work before reaching patients. We can however reasonably expect that at the expiry of this licence we will have progressed multiple new treatments along the path towards clinical development, and also eliminated some projects due to lack of effect or other technical hurdles. During drug discovery we test many different molecules in cells or tissues (also known as 'in vitro', which is Latin for 'in glass' due to the glass test tubes used historically) and in live animals (also known as 'in vivo', from Latin meaning in a living organism). The combined volume of this work is extensive and therefore we expect to publish a small proportion of the work we will carry out.

Who or what will benefit from these outputs, and how?

We expect the new medicines we will discover and develop to have significant positive impacts on the lives of patients, their families and society as whole. The new knowledge we will create and share will be of great use to other research groups in academia and in the pharmaceutical industry, and will enable other new medicines and treatments to be generated. In the short term (1-5 years) our data will

impact the progress of our internal research projects, informing decision making and also generating new ideas for further projects. Longer term (5-15 years) some of these projects will begin to reach patients and hopefully make an impact on their health. For respiratory treatments we know that the impact of this can be life changing, as small improvements in lung function (i.e. being able to breathe more easily) can bring significant improvements in quality of life, and enable patients to walk or speak without becoming out of breath. For more severely affected patients these new treatments may protect them from life threatening exacerbations, which often result in hospitalisation and death.

How will you look to maximise the outputs of this work?

We will share the new knowledge whenever we can through publications, conference posters and presentations. We have networks of academic collaborators with whom we share our findings and benefit from the discussion and validation of our findings. We are aware that there is a need to share negative findings as well as positive ones, and we will engage with others in the scientific community to understand if there may be ways to share non-commercially sensitive information that might reduce animal usage.

Species and numbers of animals expected to be used

- Mice: 3500
- Rats: 1000

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

Explain why you are using these types of animals and your choice of life stages.

Adult and aged rats and mice are appropriate animals to study respiratory diseases as they have anatomically and physiologically relevant mammalian biology. Adult animals (older than 6 weeks old for mice, 8 weeks old for rats) are fully formed and can demonstrate representative tissue and immunological responses. Aged animals (more than 40 weeks in mice, 1 year in rats) may be used as we recognise that in some respiratory diseases (such as chronic obstructive pulmonary disease (COPD)) age itself may be a factor that limits the ability of the lung to repair or regenerate and we wish to understand mechanisms that could modulate this.

Typically, what will be done to an animal used in your project?

This licence includes a variety of procedures which will be combined in study designs, but it is not intended that all animals will receive all possible steps or combinations of steps. Below are examples of the typical animal experience on this licence:

Lung inflammation

After arrival and acclimation, mice will be briefly anaesthetised to enable insertion of an identification microchip injected under the skin using in injecting needle. Five days later they would then be dosed with a new treatment directly into the lungs in a very small volume of liquid (under anaesthesia, followed by recovery). After 1 hour they would receive a challenge to the lungs via the nose (under brief recovery anaesthesia) with a substance (again in a small volume) that will trigger inflammation. Animals would be returned to their home cage once recovered from anaesthesia, closely observed to ensure they are not exhibiting any unexpected side effects, checked again at the end of the working day. If any animals are showing unexpected responses (e.g. difficulty breathing) they would be humanely killed immediately. Animals are checked again first thing in the morning. Animal weight is monitored, and due to the lung inflammation some weight loss is likely to be seen, which can vary depending on what challenge has been used, and the effect of treatments given (for example anti-inflammatory steroids can also induce weight loss). Animals reaching 10% loss will then be weighed daily and humanely killed if they reach 20%. At the end of the study, typically 24h to 7 days after first challenge, they would be deeply anaesthetised before a final blood sample is taken, usually directly from the heart immediately before being humanely killed under anaesthesia. In some studies, the animals may be challenged more than once, or humanely killed at later timepoints days or weeks after challenge. before we wash out the lung tissues to obtain a sample of cells. These studies may generally last 2-7 days and are expected to be the majority of experiments on the licence (more than 80%).

Lung inflammation involving a virus

This would be the same typical experience as above but with the additional step of introducing a virus or bug into the airways, which will induce inflammation. These studies may last 2-7 days and are expected to be a small minority (less than 5-10%) of all experiments.

Lung inflammation other agents

Sometimes we may use other agents which directly act on the tissue to cause damage, instead of triggering inflammation first. The overall experience is similar to the above examples but instead of virus or inflammatory stimulus, the animals may be given an enzyme or chemical mixture that damages the tissue directly. Sometimes this may be done by inhaling a gas that is irritating to the lung for a short period. These experiments are typically 2-3 weeks in duration and expected to be a small minority of studies (0-5%).

Studies carried out under anaesthesia without recovery

In these experiments animals are anaesthetised before any experimental steps such as dosing or airway challenge are performed and therefore do not experience any awareness of the inflammation or lung injury being induced. These studies are short, typically less than 1-2 hours and animals are humanely killed at the end before waking up. This is expected to be a small minority of studies (0-5%).

A small number of studies may use animals which are 12-20 months old during studies instead of our usual range of 2-4 months old, and they will receive additional checks on their condition (including claws and teeth) to ensure the natural processes of aging are not causing harm.

What are the expected impacts and/or adverse effects for the animals during your project?

Placing the identification tag under the skin using an injecting needle is not expected to cause any impact beyond brief discomfort. Inflammation of the airways in the ways described above is likely to be uncomfortable and animals may exhibit clinical signs of discomfort or illness such as loss of appetite, reduced grooming and reduced social interaction. Reduced food intake can lead to a body weight loss, and for this reason animals are weighed regularly (at least twice a week, daily if we see loss of 10% or more). The majority of studies we expect to conduct are short (1-7 days) although rarely some experiments can last for 10 weeks or more.

Expected severity categories and the proportion of animals in each category, per species.

What are the expected severities and the proportion of animals in each category (per animal type)?

Mice and rats:

Mild 50%

Moderate 50%

What will happen to animals used in this project?

- Killed

Replacement

State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.

Why do you need to use animals to achieve the aim of your project?

Respiratory diseases arise through complex interactions of multiple biological, genetic and environmental factors. The structural cells of the lung tissue, the underlying vascular and nervous system components, and the immune cell populations all interact in ways which cannot yet be predicted from work using just cells or isolated tissues (from patients, blood donors, immortalised cell lines or from humanely killed animals), and cannot yet replace animal studies, especially when new biological pathways which are not fully understood are involved.

Which non-animal alternatives did you consider for use in this project?

Non animal systems are a key part of our research programmes, and animal studies are only considered when sufficient data are available to justify their use or in certain circumstances where the biology is novel and not characterised sufficiently to enable in vitro simulation. Parallel teams within the organisation work on multiple non-animal technologies, including cell based assays that mimic lung tissues by growing cells in droplets so that they form small structures that are similar to the air sacs in the lung. These teams also make use of human lung tissue obtained through collaboration with

hospitals. Small pieces of the lung are sliced thinly and maintained so that they can be studied under a microscope, and the effect of novel treatments observed.

Why were they not suitable?

The cell and tissue based systems we do use are not complete representations of the lung in health or disease. Cell culture systems, even when they have some structural homology (ie they grow into shapes that look like lung tissues) such as organoid culture, they do not have the complex biology seen in living organisms where multiple types of cell and structure combine. This means they are not suitable for testing the activity of new medicines as they will not respond in a way which reflects the real biology, and we are likely to miss important effects and interactions. Human tissue, when available, is not a complete solution as it lacks exposure of the lung cells to air (they are submerged in liquid to keep them alive), blood circulation, nerve tissues, immune cell trafficking and many other components.

Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.

How have you estimated the numbers of animals you will use?

Estimates are based on anticipated throughput of studies and using numbers typically used in previous experiments. Over a 5 year period usage may vary across protocols as the demand from as yet unknown research projects emerges. Rather than defaulting to maximise the estimates across all protocols I have kept number within the range of recent experience.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

Study designs are reviewed as part of our internal statistical review system to ensure that studies use appropriate numbers of animals, and that steps have been taken to eliminate bias, such as ensuring analysis is performed blinded (i.e. the person carrying out the measurement does not know which treatments individual animals have received), and randomisation (which means using a mathematically random order to perform measurements) of animals and samples are included. Using these methods we can be confident in the conclusions we draw from the experiment.

We have selected designs which are flexible with the intention that changes in experimental design and procedural steps will be introduced based on our findings, which may enable a reduction in animal numbers, subject to appropriate statistical analysis.

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?

Much work is conducted in vitro on cells and human tissue prior to animal work, which reduces animal usage for preliminary experiments. Breeding of regular rats and mice is performed for us at an external supplier which enables the maximum efficiency of animal usage for these animals. Genetically modified mice (such 'knock-out' or 'knock-in' mice) are not bred under this licence, breeding for animal supply is carried out elsewhere under different project licences.

Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

We will use mouse and rat models which enable us to study the mechanisms involved in human lung diseases such as asthma and chronic obstructive lung disease (COPD), as well as complications such as viral exacerbations (which is when a viral infection causes a dramatic worsening in patients symptoms) which can lead to hospitalisation and death for severely affected patients. We need to induce airway inflammation and cause changes to the lung tissues which reflect these human diseases, so it is likely that animals will experience respiratory changes and discomfort that cannot be avoided. The models and methods selected cause the least pain, suffering, distress or lasting harm to the animals because we carefully design our studies to minimise or eliminate these factors. In practice this means performing experiments to identify the amount of challenge or stimulus we need to use to see a meaningful biological change, while minimising suffering. We have selected airway models that are well tolerated and are expected to result in a moderate level of severity, which includes some clinical signs such as reduced food intake and lack of grooming. Where possible we will carry out studies using anaesthetised animals that can be humanely killed at the end of the experiment instead of being allowed to wake up again, to minimise the chance of them experiencing pain.

One of the models we expect to use commonly involves the challenge of the airways directly with an agent we expect to trigger inflammation, as this mimics what is happening inside the lung of a patient with asthma or COPD. The agent is carefully introduced into the lungs of an anaesthetised animal in a small volume of liquid which rapidly spreads throughout the lung. We then monitor animals for a period and at a predetermined time we anaesthetise them and measure how well the lungs are working using specialist equipment. The animal is then humanely killed and the lung tissue rinsed out to collect inflammatory cells and other markers of inflammation. We would usually combine this procedure with pre-dosing of treatments which we expect to reduce inflammation or tissue reactions to inflammation. These treatments would normally happen without anaesthesia and could be injection into a vein or under the skin or into the abdominal cavity, or dosing into the stomach directly via the mouth or using food which has treatment added to it. Other variations of this model include making animals allergic to

the agent (for example by injection or inhalation) before introducing it to the lung so that the inflammation is similar to that seen in asthma patients.

Why can’t you use animals that are less sentient?

We are seeking to identify and develop treatments for human use and therefore although there may be some similar biological mechanisms in lower species such as flies, worms or fish, it is known that the probability of our agents working in these organisms is very low, as they are so different at a molecular level due to millions of years of evolution. In addition these lower species also do not reflect the mammalian and human immune systems and respiratory structures.

Adult and aged animals will be used, immature animals are not suitable for practical and biological reasons. Young rodents do not have a mature immune system or lung structure, which mean that experiments would not reflect the way that these cells behave in patients. The speed of development also means that in most studies animals would become adult anyway during the experiment.

This licence application does include a protocol for purely non-recovery studies where all steps are performed under terminal anaesthesia.

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?

Animals are closely monitored and are kept in modern purpose built facility with highly trained and motivated technical staff. We implement many systems to improve animal welfare, including non-aversive handling (i.e. not picking up by the tail), single use needle policy, environmental enrichments such as tunnels, nesting materials and chew sticks, as well as cage floor level access to food for animals displaying reduced activity or mobility.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?

Publications such as the Handbook of Laboratory Animal Care and Welfare (Wolfenson and Lloyd)

Our organization includes a team of statisticians who have implemented a system where animal experiments are formally reviewed before they start. This review is conducted by a researcher and a supporting statistician team to ensure the goal, experimental design, and data analysis align. This process ensures the design is robust and the minimum animals are used that are needed to answer the scientific question.

In addition, the following guidelines and online tools are also used to influence the design of our animal studies:

- The PREPARE Guidelines, found at https://norecopa.no/prepare

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?

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I receive regular updates from the Named Information Officer at the Establishment, and I am in regular contact with other scientists who work with animals and teams of animal welfare specialists within and outside my organisation. I also attend 3Rs events where we meet with local and regional partners to share our best practices. If new approaches are identified which could be implemented, pilot studies will be used to assess the impact of changes to established practice and ensure the most refined and reproducible methods are used.

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