Home Office

NON-TECHNICAL SUMMARY

Respiratory Pharmacology II

Project duration

5 years 0 months

Project purpose

- (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

Asthma, COPD, Respiratory, Disease

Animal types	Life stages
Mice	adult
Rats	adult
Guinea pigs	adult

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?

The development of therapeutic treatments for respiratory lung diseases. Initially working on the development of new vaccines against respiratory diseases. Further areas maybe added via amendment as additional programmes are developed.

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?

Asthma UK calculated that the annual cost (direct and indirect costs) of treating asthma in the UK to be £1.1 billion, at least £666 million is spent on prescription costs each year. COPD costs the UK £1.9 billion each year in treatment. According to the UK government statistics in 2018, nearly 4 million work days were lost in the UK due to respiratory conditions.

Respiratory disease affects one in five people and is the third biggest cause of death in England. There is a massive unmet need for new treatments to cure or improve the management of these diseases worldwide.

The data generated during this project will be used to select the strongest candidates for potential new treatments. Likewise, new agents could be identified with the potential of increasing the range of medicines available in the fight against respiratory diseases.

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

Research undertaken on this project licence will result in efficacy, safety and tolerability data for potential new vaccines and antibody treatments against respiratory diseases and increase the understanding of the underlining biology behind the diseases investigated.

The data generated under this project licence will be used to progress the strongest candidates into clinical development with the intention of developing marketable vaccines. In addition data will help us understand the biology behind these diseases.

Data will also be used for filing new patents and thus disseminated through the patent publication pathways.

In addition, to patent applications, scientific publications and conference presentations will be used to disseminate key scientific findings and promote the general advancement of the research studied.

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

In the first instance the data generated from studies will aid the researchers in the selection and characterisation of new vaccines and antibody treatments which will lead to their further development (e.g. in clinical trials) and could potentially lead to new therapies for respiratory diseases being introduced to the market.

Long term, these products have the potential to significantly enhance the quality of life for people suffering these chronic diseases or potentially cure them. This will benefit the whole society via reduction in absenteeism from work or school and reduction in demand on health services.

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

Our commercial client will, where not confidential, look to publish the information via scientific publications and conference presentations in addition to patent applications.

One of the key goals of our academic clients will be to publish the results via scientific publications conference presentations, in order to promote the general advancement of the fields studied.

Species and numbers of animals expected to be used

- Mice: 3600
- Rats: 3600
- Guinea pigs: 2100

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.

Mice and rats are the lowest vertebrate groups on which well characterised and minimal severity respiratory disease models have been developed. Guinea pigs are widely used for respiratory research because their airways are generally more sensitive than other rodents, especially to allergens. Mice will be the preferred species used as an experimental model of airway disease. However, the final choice will be dependent on, the specific disease area, e.g. guinea pigs are a good species to use when investigating allergic bronchial asthma and anti-asthmatic drugs because the airway anatomy and the response to inflammatory mediators is very similar to humans. Also, further work planned e.g. specific disease models (to be undertaken by the client) would affect the species of choice.

In addition, these species, especially mouse, are the long-standing choice of immunologists with lots of historical data available for hypothesis-building and predictions and have successfully identified the key operating principles of the immune system on which major clinical advances are based, e.g. the successful development of PI3Kd inhibitor for respiratory diseases.

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

After arrival all animals will be allowed at least 7 days to become acclimatised to the unit.

After which the animals will be dosed with potential new vaccines or antibody treatments. These animals may receive up to total of 28 doses. A certain proportion of the animals will be used to investigate the effects and pharmacokinetic properties of the assigned treatment after single and multiple doses. Blood samples, and tissues taken post-mortem are analysed.

The next subset of animals will used to study the efficacy of the candidate vaccines or antibody treatment. The animals will be studied in a mechanistic model of respiratory inflammation, where they are challenged with the respiratory virus the treatment is targeted for, into the lung and the efficacy of the treatment on the inflammatory response investigated.

Another subset of animals will be studied in the ovalbumin or house dust mite induced respiratory disease models of either asthma or COPD. These animals will receive one of more doses of inflammatory agents and will develop a phenotype very similar to the human diseases. The ability of the candidate vaccines to alter this phenotype will be studied.

The last subset will also be studied in the same respiratory disease models, with an added viral challenge to study the ability of the candidate vaccines or antibody treatment to reduce viral exacerbations.

A proportion of the animals in each study will receive vehicle only these will be the control animals and are the group most likely to show the possible adverse effects. From experience we know the dose of challenge agent that gives the maximum response we are measuring while keeping any adverse effects low if at all. This is especially important for these control animals.

While the maximum length a study could run for under this licence is 9 months, this would be very rare and the justification to run such a study would need to be strong. The vast majority of studies will be much short with a typically study lasting 2 to 3 weeks from starting the study to the final sampling time point. This would typically be a week of pre-dosing followed by a challenge and up to 2 weeks of sampling post-challenge.

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

Studies conducted under this licence may induce some adverse effects in some of the animals. Typical adverse effects include changes in appearance, for example, minor changes in respiratory patterns ruffled fur, or changes in behaviour, e.g. the animals may become subdued. Other effects may include reduction in body weight and/or reduced eating. The larger proportion of animals used in these studies will, however, not experience any noticeable adverse effects.

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)?

For the majority of animals, the severity level will be mild. However, as stated above, in some studies the animals may experience some adverse effects, but these would only cause the animal a moderate level of distress which will in most cases be transient.

What will happen to animals at the end of 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?

Understanding the mechanisms of action and assessing the effectiveness of potential new vaccines or antibody treatment in respiratory diseases requires the presence of a fully developed and functional respiratory system. Currently this cannot be reproduced outside of a living organism. Indeed, the assessment of the efficacy of candidates for respiratory diseases cannot be efficiently modelled in vitro due to the complexities of the lung microenvironment and the involvement of the immune system in these diseases. This cannot be fully replicated in a laboratory setting.

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

Novel vaccines or antibody treatments selected for testing in the models contained within this licence will have to have been through a defined screening cascade of in vitro assays prior to testing in vivo models to show efficacy with in vitro readouts, such as, potency/selectivity, cellular function and ADME assays. This will minimise numbers of candidates to test in vivo by implementing rigorous in vitro screening of candidates with high bars set for in vivo translation.

Why were they not suitable?

Improved in vitro screening techniques will reduce numbers of animals used by reducing the numbers of candidates that qualify for in vivo screening and will at the same time improve the quality of candidates brought forward for in vivo screening.

However, there is a point in biological research when in vitro experiments cannot provide all the necessary conditions to further research. In vitro models can mimic certain aspects of the of disease. They cannot, however, reproduce the complex interactions between different cells and mediators or reproduce the functional changes that occur as part of the ongoing disease process. The scientific community has established extensive in vitro systems to confirm the existence of a particular mechanism. But it is only with in vivo experiments that we can establish whether new medicines targeting such pathways will be efficacious and safe.

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?

A typical experiment may include up to 60 animals and we might run approximately 60 studies, for rats and mice and 35 with guinea pigs over 5 years testing new medicine candidates. Thus, the expected number of animals to be used under this licence is estimated at 3600 mice, 3600 rats and 2100 guinea pigs.

Animal numbers are calculated using the lowest numbers per group to give reliable data based on previous experience. Number of studies per year are based on current rate of studies from the previous licence These numbers may be lower if alternative methodologies to replace such studies are developed over the next 5 yrs.

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

To ensure we use minimal number of animals required to obtain meaningful and relevant data, we have extensively consulted available literature, attended experimental design and statistical courses, discussed with statisticians and NC3R staff and information provided by the NC3R.

If the defined progression point for a candidate drug is a set blood plasma level 24 hour after administration. A study need only include a very early time point, to show the drug has successfully been administered and the decision-making 24 hour time-point. Additional time-points would almost certainly not influence the candidate's progression and therefore are not needed in the study. This significantly reduces the number of animals required. Also, it allows for more than one candidate to be tested in a study, reducing the number of animals needed for control groups.

Wherever possible cassette dosing will be used in PK studies. This also reduces the number of animals required.

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

In many cases, the numbers of animals required will be reduced by longitudinal measurement of responses, e.g. by serial blood sampling or by optimised protocols to only include the key decision-making time-points.

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.

Mice rats and guinea pigs are the ideal organisms for these investigations:

They are the long-standing choice for respiratory research. There is an immense spectrum of well-characterised models developed over the years which cause minimal distress and suffering while providing meaningful data This is due to the similarities between the respiratory and immune systems in these animals and human. The commonly used laboratory strains of animals are well phenotypically and genetically characterised. Guinea pigs are widely used for respiratory research because their airways are generally more sensitive than other rodents, especially to allergens.

Secondly, because of the large number of well-characterised models, there are reagents available permitting the thorough, incisive, and comprehensive analysis of samples collected allowing for the maximum amount of information to be obtained from the experiments undertaken.

To minimise discomfort of repeated procedures such as anaesthesia, we will combine treatments under a single anaesthetic event wherever possible. The anaesthesia will preferably entail the use of inhalation agents whenever possible. Least invasive route of substance administration and needle gauge will be used where possible.

Negative control groups (baseline groups) will be minimised whenever statistically feasible.

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

The human respiratory and immune systems are intricately complex and modelling it for assessment of new medicines requires models in vertebrate animals whose systems have been studied and can be, to a good degree, compared to human. Mice, rats and guinea pigs are the lowest vertebrate group on which plethora of reliable information on the function of the systems are available and where well characterised and minimal severity respiratory models have been developed.

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

To minimise discomfort of repeated procedures such as anaesthesia, we will combine treatments under a single anaesthetic event wherever possible. The anaesthesia will preferably entail the use of inhalation agents whenever possible. Least invasive route of substance administration and needle gauge will be used where possible. Negative control groups (baseline groups) will be minimised whenever statistically feasible.

All animals will receive appropriate operative care in terms of anaesthesia and pain management both during and after the procedure.

In house expertise further enhances animal welfare, by providing close collaboration with dedicated animal care staff and veterinary consultants, and ready access to highly skilled advice.

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

We will follow the NC3Rs guidelines on the "Responsibility in the use of animals in bioscience research" and consult all the relevant references listed therein. (Reference: NC3Rs/BBSRC/Defra/MRC/NERC/Royal Society/Wellcome Trust (2019 Responsibility in the use of animals in bioscience research: expectations of the major research councils and charitable funding bodies. London: NC3Rs.

Animals will continually be monitored for signs of pain and distress, especially post-challenge, by use of the grimace scale;
https://www.nc3rs.org.uk/sites/default/files/documents/Guidelines/MGS%20Manual.pdf.

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

We will continuously monitor publications and the NC3Rs website for new and alternative models that could be implemented as part of this project. In addition, articles on advances in the 3Rs are regularly published on the internal Users News Forum and other relevant information is circulated by AWERB. Whenever possible we will implement these refinements into our studies.