Home Office

NON-TECHNICAL SUMMARY

Angiogenesis in health and disease

Project duration

1 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants

Key words

angiogenesis, skeletal muscle, remodelling, sarcopenia, hypertrophy

Animal types	Life stages
Mice	adult
Rats	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?

We have identified novel approaches to regain control over blood vessel growth that is lost in many diseases, allowing us to better understand the cells and molecules involved in regulation and devise more targeted interventions. Much of this work has been successfully addressed, but Covid-19 lockdown prevented the final experiments needed to complete studies for 2 PhD students, so we wish to have a short-term licence to continue the current licence aims, objectives and procedures.

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?

An adequate, but not excessive, blood supply is critical to health. Hence, numerous pathologies arise as a consequence of disrupted vessel growth.

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

The aims of the work are expected to be realised, given that this is a licence intended to complete the final experiments in a series already started before interruption by Covid-19 lockdown. We will continue to generate outputs aimed at wide dissemination of the results including posters and oral communications at scientific meetings, peer-reviewed articles and reviews, research seminars and public engagement events.

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

Cell and molecular biologists, physiologists and biomedical scientists will benefit from these outputs in the short term. Public understanding of science is part of the long-term goal. Adoption of the findings may influence clinical practice and aid in rehabilitation medicine.

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

Immediate beneficiaries are other researchers in the field, or other fields of biomedical research; patients with relevant pathologies and/or clinicians attempting treatment; society as a whole due to the social value of new knowledge, which may in time form the basis of economic benefit. Benefits will be utilised to inform better diagnosis and new treatments, or improved quality of life, based on these pre-clinical data; intellectual gain will accrue from dissemination of new knowledge, e.g. publishing in scientific journals and informing other research; these data will complete publications begun under the current PPL. The timeline of benefits will be varied: immediate benefits will be the provision of essential data to inform the next stage of the project; short to medium term benefits will accrue from published

papers to inform the scientific field; long term benefits may include major discoveries based on this original work, but the nature of scientific research cautions against making unrealistic goals on this score. Benefits will be maximised by use of data as the basis for subsequent grants, thereby continuing the process of knowledge expansion, and where possible by exploiting the intellectual property rights in conjunction with the University legal department.

Species and numbers of animals expected to be used

- Mice: 36
- Rats: 48

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.

We are using animals previously demonstrated to exhibit similarmechanisms of muscle hypertrophy/atrophy as seen in humans, which will allow us to explore new ways of supporting exercise tolerance in conditions where mobility is limited.

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

For some animals, they will be put to sleep and one hindlimb muscle removed; this may occur in humans following disease, cancer or a traffic accident.

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

We take care to administer pain relief after surgery, and the animals recover very quickly - indeed, they have been observed hanging upside down on wire cage lids within 24 hours, suggesting there are no serious impediments to locomotion and routine activity.

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)?

All surgery is classified as being of moderate severity; 20 years experience has suggested little difference in animal response among categories.

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?

By careful monitoring of outcomes, we have managed to reduce the duration and intensity of muscle activity required to elicit vessel growth, have refined the interventions to reduce the discomfort, but as we are investigating a complex integrated response have not yet found a suitable alternative to use of whole animal models. As this project seeks to complete two PhD studies interrupted by Covid-19, it would be inappropriate to adjust any procedures at this stage.

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

N/A

Why were they not suitable?

Biology is inherently complex, and development of sustainable therapy cannot rely on simplistic models.

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?

We have many years experience using these animals with these or similar interventions, and seek to use the minimum number that will provide robust data: ambiguous findings arising from the use of inadequate sample size to allow appropriate statistical analysis would be a waste of animals.

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

We have previously engaged the services of biostatisticians to ensure weare using adequate, but not excessive numbers of animals. Our long experience in conducting such experiments has demonstrated the validity of this approach, in that our findings have been replicated by other laboratories around the world.

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

We always attempt to derive as much useful data from each animal, to both maximise the benefit derived from each animal used but also to minimise the use of additional animals. This may take the form of tissue samples used for two different analyses, or measurements made under terminal anaesthesia followed by ex vivo experiments.

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 use a model of inducing muscle hypertrophy that is consistent with the extent of compensatory growth seen in a number of clinical conditions, without inducing pathological responses as seen in some alternative methods. For development of obesity and complications we use a strain of rat that spontaneously develops this condition.

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

We have demonstrated over a number of years that the biological responses we are studying are conserved among mammals, but there is little evidence to suggest less sentient animals would have the same response. As the therapeutic goals are aimed at muscle dysfunction most typically experienced in adult life, using immature stages would be inappropriate as we know there are mechanisms aiding recovery that are lost with age. The response we are studying are part of a dynamic remodelling process, and hence require chronic intervention, beyond the scope of anaesthetic insensitivity.

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

This is the final stage in an established research program, so further adjustment to procedure would invalidate much of the data generated from animals used so far, so would violate our commitment to upholding the 3Rs principles.

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

We follow current advice from the Home Office regarding regulatory procedures and advice, and follow current standards laid out by reputable biomedical science journals.

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

We subscribe to relevant sources of reliable animal welfare advances, such as Understanding Animal Research and the National Centre for the replacement, Refinement & Reduction of Animals in Research, and communication with local named veterinary surgeon and animal care staff.