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NON-TECHNICAL SUMMARY

Retinal Disease Pathology and Treatment in Lysosomal Disease

Project duration

2 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
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants

Key words

Gene Therapy, Retina, Lysosomal Disease, AAV

Animal types	Life stages
Mice	Embryo and egg, Neonate, Juvenile, 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 overall goal of this project is to develop a gene therapy for a sub-type of an inherited eye condition called retinitis pigmentosa (RP), specifically caused by mutations in a gene called HGSNAT. This gene is involved in the breakdown of sugars in the body and, when mutated, causes a build-up of waste products that seems to particularly effect the light sensitive tissue found at the back of the eye, known as the retina.

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?

There are currently no therapies available for HGSNAT-associated RP. The overall goal of this project is to develop a gene therapy by treating the mouse model of this disease with a harmless virus (adeno-associated virus or 'AAV') designed to restore HGSNAT expression function to the retina.

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

Short-term benefits: In the short term, we will produce data that will indicate whether gene therapy can treat the retina in HGSNAT-associated RP in the mouse model.

Medium Term: Further development gene therapy for HGSNAT-associated RP and potential development of further therapies for retinal disease caused by mutations in lysosomal enzymes.

Long term: Clinical trial, in humans, of AAV gene therapy in HGSNAT-associated RP.

We expect to publish our work in scientific journals and at conferences and to be able to generate new patents around methods of treatment and either commercial licences or a spin out company to take these advances forward into patient therapies.

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

The main beneficiaries of this project will be the patients who have been diagnosed with RP due to HGSNAT mutations. By the end of this project (short-term benefit), we will have produced data that indicate if an AAV gene therapy can restore function to the retina in our mouse models. If positive, this data will support clinical trial applications to regulators in both the UK and USA. In the medium term, we may need to run more studies following advice from regulators. Longer-term, we would hope that within the next 5 years, from the commencing of this project, we will have started a clinical trial.

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

We will maximise outputs through several means. We will collaborate with other research groups to generate and share knowledge of these diseases and models. We will look to publish all findings, even when unsuccessful in open-access journals which ensures that the maximum number of people can access the data. In particular, the publishing of unsuccessful results is important in ensuring other groups do not waste time, resources and animals by pursuing strategies that have already proven unsuccessful. We will disseminate knowledge through conference presentations, publications and through discussions with patients.

Species and numbers of animals expected to be used

- Mice: 500

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 are the least sentient species in which models for lysosomal diseases exist and provide some of the best available models of human lysosomal disease progression. These models have been well characterised by our group and others. Therefore we know a lot about the disease progression and how to mitigate symptoms.

Although there are zebrafish models available where the gene(s) we are interested in are deficient, the use of these models for the development of gene therapies is difficult. This is primarily due to the fact that zebrafish have an increased capacity for retinal cell regeneration, which could mask the effect of a gene therapy treatment.

Mice are used between 1 month of age and a maximum of 9 months of age. We have previously characterised the retinal disease in the mouse model between 2 and 9 months and shown a clear and progressive degeneration. Mice are a standard animal for performing ocular gene therapy studies and the protocols we use have been developed and standardised for decades.

In summary, we have extensive experience with the mouse model, we know the model develops retinitis pigmentosa, we know the timescale for this and we have techniques that have been refined by ourselves and other groups over decades. This, combined with un-suitability of alternative animal models such as zebrafish, is why we are using mice for this work.

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

Typical protocols for rodents include:

1) Delivery of therapies: A 1-2 month old animal may receive one injection of a therapeutic substance in each eye, e.g. A mouse is anaesthetised and then an AAV vector is injected into the eye. Typically mice will only be given one injection in each eye with no repeat injections and this does not cause extensive pain or stress. Mice quickly recover from these injections (typically within 24 hours) and injections can be performed in a time-efficient manner which reduces the length of time the animal is under anaesthesia (typically <15 minutes). Animals may have retinal imaging under anaesthesia during the follow-up period and may also have samples of bodily fluids (blood, saliva, urine) taken to analyse the effects of treatments and/or the health of the animal on up to 10 occasions.

Animals will typically be given eye injections (with appropriate treatment) and followed up for up to 9 months of age. Animals are always monitored closely throughout the length of the experiment to ensure good health and any signs of pain, distress or ill-health are addressed accordingly (pain-relief, antibiotics, creams, etc). At the end of the experiment the animals are humanely killed and organs are typically harvested for further analysis.

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

The mouse models we will use develop a form of retinitis pigmentosa. This is a progressive retinal degeneration which, in our models, starts from about 2 months of age. However, the function of the retina remains present up until about 6 months of age, therefore prior to this there is little functional impact on the ability of the mice to see. Furthermore, mice are less reliant on their sight than humans so we do not expect any welfare concerns to arise due to the retinal degeneration. The models that we work with can develop other, non-sight related, symptoms such as urine retention – but only as the mice get to 8-9 months or age – past the age they would be used on this project. Should any animals develop these symptoms will consult with the named veterinarian for appropriate course of action.

Expected adverse effects include weight loss (following treatment), pain following injections (which is mitigated with painkillers), lethargy and abnormal behaviour. Animals can experience stress due to restraint and handling which will typically resolve by the end of the procedure. Where animals require anaesthesia, they will experience transient discomfort from induction of anaesthesia. Animals may undergo anaesthesia on up to 12 occasions for retinal imaging and once for eye injections (<15 minutes). Sometimes, during the injection the animal’s breathing can seem laborious due to anaesthesia, this typically resolves by the end of the injection, once the animal recovers from anaesthesia. There is also potential for infections in the eye following injection. This can be mitigated by good injection technique, ensuring that all instruments are sterile and a new needle is used for each injection. We will monitor for any signs of infection and give appropriate treatment (e.g. antibiotics) in consultation with the named veterinarian..

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)?

Expected severities will be mild to moderate, In breeding protocols 75% of mice will experience sub-threshold harms, 25% mild and 0% moderate. In experimental protocols 20% will be mild and 80% moderate. Overall, as most mice fall into breeding protocols - we expect 50% of mice to be sub-threshold, 20% of mice to be mild, and 30% moderate.

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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?

The conditions we work on are complex and are influenced by a host of different factors. Many of these conditions are neurological in nature and primarily affect the eye. As such, non-animal alternatives, such as cell-based tests, may not be appropriate as they can only provide limited results. We have recently described the eye disease in the mouse model and we now know that the mouse mirrors the human disease, giving us physiological data which cannot be achieved using cells in a dish. Our therapies are assessed with a variety of outcome measures such as imaging and tissue sampling which can only be achieved with animal models.

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

Performing a Bimmoh (https://bimmoh.eu) search, on the 7th of July 2026, for ‘retinitis pigmentosa’, returned ~200 papers describing non-animal alternative, primarily based on cell-based assays in the lab (iPSC-derived retinal organoids and photoreceptor cells, immortalised cell lines, etc). Bimmoh is a scientific search engine designed to curate information about different biomedical models. Whilst these non-animal alternatives are useful to reduce the number of animals used (and a number of them will be used by our lab prior to performing animal studies), in the case of HGSNAT-associated RP, these aren’t able to fully replace animals as they fail to comprehensively recreate the disease phenotype. Furthermore, often the AAVs that we use will be able to treat cells in a dish, however when injected into animals (or indeed humans in clinical trials), vectors have to navigate multiple barriers that are not present in the lab (other non-target cell types and membranes that have evolved to protect the retina. There are no suitable alternatives that are therefore relevant to distribution, delivery of treatments into the eye and potential immune system responses that play a part in the progression of disease.

Why were they not suitable?

No adequate tissue culture models of the complexity required to examine retinal preservation, following gene therapy, in living organisms exist. In order to better predict what treatments will prove to be effective and safe – we require animal models to test these approaches. The eye is a complex system, comprised of multiple different cell types, and multiple different barriers to entry of our AAV treatments which are currently impossible to model in tissue culture and/or computationally.

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 based these numbers on our previous experience working with these models and the numbers used on previous licences. As a part of this project, there will be a maximum of 2 rodent lines running at any one time.

We can estimate that we will typically need 8-11 mice in each group to see differences between treated and untreated mice (by analysing the structure of the mouse retina and markers in bodily fluids/tissue) and we would typically have 3-6 groups. We also have an accurate idea of how many experiments we would like to complete over the course of the 2 years that this licence will run. We expect to evaluate 1-4 different AAV vectors for treating HGSNAT-associated RP.

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

We will use statistical methods to calculate the number of animals needed for our experiments. We also use tools such as the NC3Rs design assistant to help design experiments. We will also perform as much work as possible in non-animal models, such as cell culture experiments, to further reduce the number of animals needed. For example, we will test AAVs in a cell culture system to ensure that they can successfully deliver the HGSNAT enzyme prior to then injecting them into mice - this reduces the number of AAVs used, and subsequently the number of mice used.

In order to monitor retinal degeneration throughout the lifetime of the animal, we will use repeat retinal imaging to reduce the number of animals that we have to cull at set time points. The alternative to this would be to start with a much larger number of animals and cull a group’s worth of animals (8-11 mice) at set timepoints so that we can harvest eyes and analyse the retina in the lab. As we are interested in looking at 3-4 timepoints this would be a large number of animals in total. Doing repeated retinal imaging (e.g. OCT) allows use to use the same animals at each timepoint. This means that we reduce wastage and also allows paired data analysis to reduce between animal variation.

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

We will breed animals in such a way that the number of animals from each mating is optimised and we will collect data throughout the lifespan of the animal to generate the maximum amount of data and reduce the number of repeat experiments needed. Were possible we will utilise imaging and sampling techniques throughout the lifespan of the animal, reducing the need to sacrifice animals.

Refinement

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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.

To achieve the objectives set out in this project licence we will need to breed the mouse model of HGSNAT deficiency. This is the best mouse model of this disease. We have previously analysed the mouse model and demonstrated a significant retinal degeneration that starts around 2 months of age and progresses up to 9 months of age. This mimics what can be seen in patients, albeit with an earlier onset.

The methods utilised in this project include eye injections - a procedure that is well tolerated, offers access to the retina with limited damage to the eye itself (injection sites typically resolve quickly) and can be performed in a time-efficient manner which reduces the length of time the animal is under anaesthesia (typically <15 minutes). We will use 'Optical Coherence Tomography' (OCT), an imaging procedure that is non-invasive, allowing imaging through the cornea (transparent layer at the front of the eye) towards the retina at the back of the eye. Along with OCT, we will use electroretinograms (ERGs) which are relatively non-invasive, involving an electrode being placed across the retina to measure electrical activity in the eye. Occasionally the electrode may cause a scratch on the cornea, however this typically resolves. Sampling methods, such as blood sampling, will always use the less invasive approach.

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

Mice are the least sentient species in which models for this condition exist and provide some of the best available models of human disease progression as we have shown previously. Although we could start by treating models, such as zebrafish, to show proof of mechanism it can be difficult to test ocular therapies in zebrafish, due to zebrafish’s retinal cells having a greater ability to regenerate naturally. We will need to recover animals following eye injections to allow monitoring of treatment. We will also need to recover animals after imaging procedures, again so we can follow the progress of the same animals throughout their lifetime - allowing us to reduce overall animal use.

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

We always look to improve the way we perform procedures. All procedures are undertaken using good aseptic technique to minimise the risk of infection. Post-operative care will involve constant monitoring in the weeks and months following procedures. Animals will be weighed and assessed for pain and distress. Analgesia (pain relief) and other treatments will be used if necessary and in consultation with the vet. Previous refinements we’ve implemented include increasing weight monitoring even past the minimum defined in our licence and performing multiple non-invasive imaging procedures in the same session to reduce the number of times an animal needs to be under anaesthetic.

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

All our experiments will be conducted following PREPARE guidelines, OECD protocols. We will refine routes and substance volumes in accordance with guidelines set out by Morton et al, 2001. Results will be reported in accordance with ARRIVE guidelines.

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

We liaise with colleagues in the animal facility within the establishment who keep us up-to-date on advances in the 3R’s via a monthly newsletter. We also have the establishments 3Rs Manager and Named Information Officer (NIO) who we consult on such matters. We can access the NC3Rs and other welfare body's websites for training information. In particular performing searches on the NC3Rs website for ‘opthalmology’ or ‘retina’ brings up articles and advice on recent advances that we can implement into our research. We will also seek to attend seminars and other educational events to further this knowledge as well as reading publications and outputs of colleagues.

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