Home Office

NON-TECHNICAL SUMMARY

Treatment of abnormal retinal development

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
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants
- (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 following aims mentioned in paragraph (b)

Key words

Albinism, Treatment, Visual Function, Retinal Development

Animal types	Life stages
Mice	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 aim of this project is to demonstrate, using albinism as an example, how to develop precision medicine pathways to prevent any child who has inherited a retinal form of blindness from losing their sight.

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?

Inherited eye disease is one of the most common causes of childhood blindness, affecting circa 420,000 children worldwide, with the numbers of children that have reduced visual acuity/visual function (but not meeting criteria to be registered as blind) likely to be much higher. Oculocutaneous albinism (OCA) is an example of an inherited eye disease that illustrates why the control of blindness in children is a high priority within the World Health Organisation's VISION 2020 — The Right to Sight programme. Albinism affects up to 1 in 1000 people and is characterised by pigment deficiency of the skin, hair and/or eyes, abnormalities of retinal development and visual impairment. The average best-corrected visual acuity (VA) in OCA is below the UK eyesight standard for driving. Moreover, there are significant effects on school performance, employment and quality of life and most patients are registered as sight impaired in the UK. Despite significant advances in understanding the molecular basis of inherited eye diseases e.g. albinism, there remains a paucity of effective treatment options. This project aims to remedy this deficit.

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

By the end of the project we hope to have established:

1. Why the retina does not develop normally in albinism. This information will be used to direct future research in this area.

2. Proof that a chemical called Pigment Epithelial Derived Factor (PEDF) can potentially be used as a precise and targeted treatment for albinism.

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

The biggest potential beneficiaries of this research will be the infants and young children with albinism, their family and society at large. Albinism is a condition characterised by pigment deficiency and

abnormal retinal development which results in a significant degree of visual disability. The average best-corrected visual acuity in oculocutaneous albinism is below the UK minimum eyesight standard for driving. This negatively impacts on the child's overall development, schooling, employment and quality of life. To date, infants and young children with albinism have been deprived of an effective treatment. This study aims to remedy this deficit by performing a thorough evaluation of potential treatments that have the potential to improve retinal development and optimise visual function in infants and young children with albinism. It will provide valuable guidance on the optimal treatment interval and the risk of complications. Each treatment has the potential to be evaluated in human clinical trials within the next 5 to 10 years.

In addition, the information from this project, including the study protocols, will be made freely available via publication in peer-reviewed journals, to benefit other researchers who are involved in the development and assessment of novel therapeutics which target abnormal retinal development in early childhood.

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

Public Engagement & Education

Our approach towards developing an effective treatment for albinism serves as an excellent example of how clinical observations at bedside can be taken back into the laboratory for more detailed mechanistic investigations and novel therapeutics development which can then be translated back into clinical practice. This is a good story which we will disseminate to the public through outreach activities, press releases etc. Those affected by the condition (sufferers and parents) will be especially interested, and we will make efforts to reach this audience. We will communicate the progress of our study to the patient community on a regular basis in conjunction with our patient and public involvement (PPI) study group. The results will be presented to the patients by liaising with patient focus groups including the "Albinism Fellowship" and "Nystagmus Network, UK". This will include attendance at the annual Nystagmus network UK open day, where patients, parents and carers will be informed of the progress of the study. The results will be publicised in the Nystagmus Network webpage and through "Focus" a publication that is distributed to all members of the Nystagmus Network. We will also utilise social media resources such as Facebook and Twitter feeds to disseminate up-to-date information about the study.

Communication of findings to the scientific community will be disseminated by presentations at national and international conferences such as the annual meeting of the Association for Research and in Vision and Ophthalmology (ARVO) and the Royal College of Ophthalmologists (RCOphth) annual meeting in addition to publications in peer reviewed high impact ophthalmological and medical journals. In addition to publication, the results will also be communicated on server lists such as the UK Paediatric Ophthalmology Server list or the North American Neuro-ophthalmology Server list. Progress of the study and results will be regularly disseminated at ongoing teaching events and public lectures. Our press office will also publicise the results.

Species and numbers of animals expected to be used

- Mice: 220

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.

In order to establish new treatment options for infants, young children and adults with albinism, it is necessary to precisely define the optimal age, drug and dose parameters that will improve eyesight without causing side effects, specifically for each genetic subtype of albinism. In humans, albinism is a genetically mixed group of conditions, making it extremely difficult to identify the specific genetic subtype at an early age, and limiting the precision with which the optimal treatment age, drug and dose parameters can be determined. In order to overcome this obstacle, we are trialling these treatments in mice that are already well-established models for each genetic subtype of human albinism of interest. Using these mice, we can evaluate, with precision, the safety and effectiveness of all potential treatments, from birth through to adulthood, for each genetic subtype of albinism.

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

A typical mouse (approximately 3 to 4 weeks of age) will receive a treatment, which may be given orally, dissolved in their drinking water, given as an eye drop or a single injection into the eye (like the injections given to humans to treat age-related macular degeneration). This mouse's eye development and eyesight then needs to be checked and followed over time. The eye development can be checked using a non-invasive retinal scanner called an optical coherence tomography (OCT). The mouse optical coherence tomography (OCT) is an adapted version of the human optical coherence tomography (OCT), which allows us to take highly detailed images of the retina. In order to measure eyesight, we will use electroretinography (ERG), which measures the electrical activity being generated by the retina in response to light, a bit like how an EEG measures brain activity. The mouse will have up to six optical coherence tomography (OCT) and electroretinography (ERG) examinations at: 4 weeks, 5 weeks, 6 weeks, 2 months, 3 months & 4 months of age, so that we can monitor how their retina and eyesight develops over time. These examinations will be carried out while the mouse is asleep under general anaesthetic. This is to minimise any possible distress of discomfort that the mouse may experience.

Like infants who like to follow stripes and patterns, mice also have the same reflex. We can use this reflex to check how well the mouse is seeing when they are awake. In order to do this, the mouse stands on a central platform. Black and white stripes of varying thicknesses are rotated around the mouse. If they see the stripes, they move their heads to follow it. The finer the stripe that the mouse follows, the better their eyesight. We will do this test three times at 2, 3 and 4 months of age.

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

The procedures planned in this project are expected to cause no more than mild transient pain or distress and no lasting harm.

It is possible that some mice may experience side effects from their medication e.g. eye infections, raised eye pressure, loss of appetite and weight loss, involuntary movements of their limbs, insomnia and sleep disturbances. This is expected to be rare. In order to minimise this, affected mice will quickly receive routine medical treatment appropriate to the presenting symptoms. Advice will also be sought from the NVS or NACWO. Any animal that is in chronic pain or distress, which cannot be relieved, will be immediately euthanised.

Behavioural and neurological tests may cause temporary (a few minutes) distress to animals, however, to limit/avoid such distress, mice will be allowed to adapt to the environment prior to testing.

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)?

The expected severity for 90% of the animals in this project is expected to be moderate, as each treated mouse will have up to six separate examinations under anaesthetic throughout their lifetime. The remaining 10% (i.e. animals not undergoing several repeated examinations under general anaesthetic over time) are expected to be mild or non-recovery. These mice will have had at most only 1 procedure/treatment under general anaesthetic and a maximum to 3 behavioural assessments before undergoing a final assessment (or their only examination) under general anaesthetic before they are culled for tissue for examination.

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?

1. In order to establish new treatment options for infants, young children and adults with albinism, it is necessary to precisely define the optimal age, drug and dose parameters that will improve eyesight without causing side effects, specifically for each genetic subtype of albinism. In humans, albinism is a genetically mixed group of conditions, making it extremely difficult to identify the specific genetic subtype at an early age, and limiting the precision with which the optimal treatment age, drug and dose parameters can be determined. In order to overcome this obstacle, we are trialling these treatments in mice that are already well-established models for each genetic subtype of human albinism of interest. Using these mice, we can evaluate, with precision, the safety and effectiveness of all potential treatments, from birth through to adulthood, for each genetic subtype of albinism.

2. To provide post-mortem ocular tissue to help us to investigate exactly why the retina does not develop normally in albinism, and how we can potentially develop effective new treatments for based on this information.

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

We considered evaluating the treatments in cells and tissues that are grown in the lab.

Why were they not suitable?

Demonstration of improvements in both retinal development and eyesight in albinism in response to potential treatments can only be achieved using live animals with a visual system (which includes eyes that receives information from a visual stimulus through the retina and then transmits this information through the optic nerves to the brain to be processed). Objective measurements of visual function can be obtained by measuring the electrical signals received in the brain. Subjective measurements of visual function can be obtained by observing the movements of the animal in response to a moving visual stimulus i.e. horizontal or vertical black and white stripes presented on a screen.

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 based our estimates on information and ranges that have been reported before about the reliability of each assessment that we are using to assess retinal development and eyesight. This gives us the minimum number of animals needed for each experiment to confirm significant differences or treatment effects. We have added a margin of 10% and rounded up to the nearest 10 to arrive at the numbers provided

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

The design of individual experiments will be optimised to ensure that the maximum amount of data is obtained from the minimum amount of resources. A randomised block design will be used to determine treatment allocation and a mixed cross-sectional & longitudinal study design has been planned which will minimise the number of animals needed for this project.

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

The male mice in this project are not being used for longitudinal assessments of retinal development and eyesight following treatment, as they can experience severe side effects from having repeated anaesthetics. Rather than letting these mice go to waste, they can be used to increase our understanding of why the retina develops abnormally in albinism and how we can potentially use this information to develop other new treatments in albinism. Therefore, we have planned the study such that a subset of male mice are killed at different ages/time points following treatment so that we can investigate the effects of each treatment on retinal development at the cellular level.

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.

For this study, we will be using genetically well characterised animal models of human albinism, including oculocutaneous albinism (OCA) type 1 in which preliminary data exists for the use of oral L-DOPA (Levodopa) (including drug dosages and formulation) in safely rescuing retinal function and ocular albinism (OA). Apart from the lack of pigment in the skin, hair and eyes and visual impairment, these animals are otherwise healthy and do not experience any pain or distress with their condition. This making them an ideal model for longitudinal monitoring of in vivo retinal development and eyesight in response to different therapeutic candidates.

With each treatment we are monitoring eye development and eyesight over time, using non-invasive methods. Eye development can be checked using a non-invasive retinal scanner called an optical coherence tomography (OCT). The mouse optical coherence tomography (OCT) is an adapted version of the human optical coherence tomography (OCT), which allows us to take highly detailed images of the retina. This represents a significant advancement on more traditional histological methods, which can only examine retinal structure at a single time-point and would require many more animals in order to obtain the same volume of data. In order to measure eyesight, we will use electroretinography (ERG), which measures the electrical activity being generated by the retina in response to light, a bit like how an EEG measures brain activity. Like infants who like to follow stripes and patterns, mice also have the same reflex. We can use this reflex to check how well the mouse is seeing when they are awake by performing OptoMotry™ examinations. This test is easier to complete and is much less stressful to the mouse in comparison to carrying out eyesight testing using a water maze.

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

In order to determine treatment efficacy, we need to perform longitudinal electroretinography (ERG), optical coherence tomography (OCT) and OptoMotry assessments of retinal, development, structure and function. These tests can only be performed in animals to whom we can:

1. Administer oral, topical or systemic medications

2. Perform longitudinal electroretinography (ERG), optical coherence tomography (OCT) and OptoMotry assessments

The tests have been specifically designed and optimised for mice and requires animals that have reached a sufficient stage of maturity and cognitive capability for the tests to be performed safely and reliably.

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

To minimise any possible distress, the functional & anatomical effects of administering potential treatments to mice at different ages on retinal development will be determined by performing longitudinal, non-invasive electroretinography (ERG) & optical coherence tomography (OCT) examinations under general anaesthesia. Animal suffering will be minimised by ensuring that all researchers handling the mice have been appropriately trained (e.g. ensuring the the ERG and OCT equipment has been optimally set up) and meet continuous professional development (CPD) requirements in accordance with ASPA guidance. All animals undergoing any form of examination will be studied for a maximum of 30 minutes per session and will be given appropriate rest periods (a minimum of one week) between examinations. Local and general anaesthetic will be administered for surgical procedures e.g. intravitreal injections followed by systemic analgesia, if required. Mice undergoing surgery will be given an appropriate rest period before further study, typically one week according, or when animal resumes normal behaviour (eating and drinking) according to established protocols.

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

We will conduct all our experiments in accordance with the most recent guidance from the NC3Rs. These are available on the NC3Rs website: https://nc3rs.org.uk/3rs-resources. We also receive a monthly electronic NC3Rs newsletter and an electronic Norecopa (Norway's National Consensus Platform for the advancement of "the 3 Rs") newsletter 7 to 8 times a year (https://norecopa.no/about/) which ensures that we are updated with regards to any new refinements that can be applied to our experiments.

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

Throughout the project, we plan to stay informed about advances in the 3R's using a combination of several online resources examples of which include the NC3R's website: https://www.nc3rs.org.uk/3rs-resources and the resources and databases listed on the European Commission’s website: https://ec.europa.eu/environment/chemicals/lab_animals/3r/key_resources/search_en.htm and https://ec.europa.eu/environment/chemicals/lab_animals/3r/key_resources/databases_en.htm.

In order to implement these advances effectively, we plan to:

1. Disseminate them to all members of the team
2. Incorporate them into our training
3. Embed them where possible into our local experimental guidelines and protocols.