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NON-TECHNICAL SUMMARY

Discovery of novel therapeutics for the treatment of neurodegenerative disease

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

Key words

Neurodegeneration, Dementia, Drug discovery, Alzheimer's disease, Parkinson's disease

Animal types	Life stages
Mice	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?

Our goal is to find new ways to treat brain diseases such as Alzheimer's disease and Parkinson's disease. We aim to discover new substances that use these mechanisms and then use animal models to test them.

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?

Neurodegenerative disorders are a group of brain diseases which include Alzheimer's disease, Parkinson's disease, Motor Neuron disease, Huntington's disease and a number of similar conditions. They are a significant global health problem. There are already approximately 50 million people worldwide with Alzheimer's disease, the most common of these conditions, and as the general population ages, this has been predicted to increase to 150 million by 2050. These disorders cause an increasing burden to sufferers through dementia and disability, which in turn impacts their caregivers and society as a whole through the cost of healthcare.

Despite some recent advances, there are currently no widely available treatments that stop or reverse the progression of neurodegeneration. Our project aims to identify treatments that have the potential to be developed as drugs for these disorders.

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

Information on potential targets for drug discovery

Our first objective is to identify novel drug targets. These are the molecules in the body which drugs interact with to exert their effects. We need to validate drug targets by demonstrating that interfering with their action causes the appropriate changes in an animal model, including reducing the symptoms of disease.

- A successfully validated drug target may be the subject of a drug discovery project for further investigation as part of our internal program.
- If a drug target is validated, but we do not have the expertise within our institute to carry out the necessary work to progress it, or if the data suggest that it would be more suited to a different disease area (e.g. stroke or cancer), then we may look for partner to progress the project, or publish our findings.
- Validation of a particular target may be unsuccessful, but our data may indicate that the target molecule forms part of a pathway which may include other possible drug targets which may be

worth investigating.

- Where target validation is unsuccessful, this information will also be made publicly available through publication, particularly where there is broader interest in the biology, for example in other disease areas, which could lead to important research or drug discovery efforts elsewhere.

Demonstration of efficacy in disease models

The second objective is to discover drug-like molecules that may interact with the drug target and to show that these molecules reduce disease symptoms in animal models of neurodegeneration.

- If a drug discovery project results in a novel drug-like substance with efficacy in a relevant model for dementia, this will initiate efforts to further develop it towards clinical testing in humans, for example through partnership with a pharmaceutical company.

- Substances that do not achieve efficacy but nonetheless have appropriate drug-like properties may be repurposed for use in other disease areas or as tool compounds for research.

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

Data on new drug targets may be available in the short term and will benefit our Institute through feeding into more long-term objectives or may benefit the wider field on neurodegenerative disease. We collaborate with other groups working in the same field and may share data, tissue samples or sections, reagents and animal models with these groups. (1-5 years).

Favourable data on efficacy that leads to clinical research will take longer to generate but may have a major impact on drug discovery for neurodegenerative diseases, due to the current lack of research in this area within the pharmaceutical industry. (3-10 years).

It is our intention that treatments we develop will eventually reach approval as drugs for one or more neurodegenerative disorders. The likelihood of this occurring is relatively low but the benefits to society would be considerable. (10-15 years).

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

Our institute is an academic group with expertise in preclinical drug discovery methodologies used within the pharmaceutical industry and applying these in an academic setting. We work with a wide network of collaborators in the academic sector to investigate and validate interesting and novel drug targets and have strong connections within the pharmaceutical industry to facilitate the eventual development of these ideas into drugs to benefit patients suffering from neurodegenerative disease.

As an academic group we seek to publish our findings whenever possible.

Chemical structures of molecules originating in our laboratory and the properties of these molecules may be published in the form of patents. This is necessary to protect intellectual property but also provides a valuable source of information on the viability of drug targets and chemical structures and activity to the wider pharmaceutical industry.

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Where projects are unsuccessful or no longer of interest to us, we will seek every opportunity to disseminate the work at scientific and public meetings as well as publish data in scientific journals.

Species and numbers of animals expected to be used

- Mice: 2850

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.

All of the procedures on this project will be carried out using adult mice.

We use wildtype (genetically normal) mice for many of our studies, but some of the mice that we use are genetically modified to develop some of the features of neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease. We may need to keep these animals until the point at which they begin to display disease symptoms such as difficulty walking.

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

There are several different scenarios which a mouse may experience, the following are examples:

Example 1: Mice will be given a single dose of a substance by injection into the abdomen. After an interval of up to 48 hours the mouse will be given a terminal overdose of anaesthetic by injection into the abdomen and a blood sample withdrawn from the heart. This is the most common type of study covered by this project licence.

Example 2: Using mice which have been genetically modified to produce one of the abnormal proteins found in the brains of Alzheimer's disease patients, we will allow them to age to four months before starting the study. They will then have their food intake reduced and be trained to carry out a behavioural test to receive a food reward when they touch the correct image on a touchscreen. At five months of age the mice will undergo surgery to inject a virus into the brain which reduces the amount of a protein in the brain which we want to investigate as a target for drug treatment. At eight months of age, the mice will be tested again for their ability to carry out the behavioural task. After several further weeks of behavioural testing the mice will be deeply anaesthetised and killed by injecting a substance into the heart and allowing it to flow through the circulation to preserve the tissues.

Example 3: Mice which have been genetically modified to produce one of the abnormal proteins found in the brains of Alzheimer's disease patients will have behavioural tests carried out at two months of age to assess their ability to recognise an object when it is presented to them, and the time taken to cross a narrow beam. Beginning at three months of age, the mice will be dosed with a novel substance that we are investigating as a possible treatment for neurodegenerative disease. The substance will be

mixed with the animals' food and given daily for eight weeks. During the treatment period we will restrain the mice and collect a small blood sample from the tail vein on four occasions. During the final week of treatment, the behavioural tests will be repeated after which the mice will be humanely killed and tissues collected for analysis.

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

Dosing either by injection or through a feeding tube and blood sampling will cause mild pain and/or distress to an animal, but this will be short-lived.

The techniques used for behavioural testing in this project are not expected to cause pain or distress other than transient stress due to being handled. For some behavioural tests the animals' food is restricted. This will lead to weight loss, but the general condition of the animals is not expected to be affected in other ways.

Surgical techniques involve a greater degree of pain and distress which may last for a few days after surgery. Pain relief will be given routinely to animals undergoing surgery. Occasionally (less than 2%) a surgical wound may fail to heal properly, in which case the named veterinary surgeon will be consulted. One attempt may be made to re-close the wound if this is within 48 hours of surgery, otherwise the animal will be humanely killed.

Most genetic alterations to animals used in this project do not result in any apparent change to the wellbeing or behaviour of the animals. In some of the disease models that we use, genetic alterations do lead to a reduction with age time in the animal's ability to function normally, especially where these lead to impairments in the animal's movement (e.g. loss of balance and coordination, tremors). Typically, these symptoms worsen over a number of weeks (depending on the model). Once symptoms appear, mice are monitored at least three times per week, and the mice are humanely killed when specified limits are reached.

Dosing of substances to induce disease symptoms may result in similar changes to the genetically altered models mentioned above. We will monitor these animals in the same way and apply the same limits before humanely killing the animals.

Some of the substances we dose will be completely novel and may have potential unknown side effects. These substances will be dosed at low doses initially and the animals will be closely observed for any adverse effects before we proceed to higher doses.

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 severities are mild (approximately 75% of mice) and moderate (approximately 25% of mice).

What will happen to animals used in this project?

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- 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?

When investigating novel drug treatments for disease it is necessary to understand how manipulation of the target for the drug impacts on the biology of the whole animal. There may be unwanted effects of drug treatment in other tissues or organs which would indicate a risk of side effects if the drug were to be dosed in humans. Furthermore, we need to gain a thorough understanding of what happens to the drug when it enters the body, including the rate it is absorbed from the gut into the bloodstream, where it is distributed in the body and how quickly it is eliminated.

When considering the effects of drugs or manipulating drug targets in the brain it is important to recognise the unique complexity of this organ, with many different cell types and networks of connections between nerve cells which cannot be fully replicated outside a living animal. Furthermore, if we want to understand how potential drugs may impact on symptoms of dementia, we need to be able to test their effects on learning and memory in mouse models of disease.

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

We already employ alternatives for much of the work at our institute.

To test the activity of potential drugs we use cultured cells from rodents or humans, and cell-free tests using proteins made in the lab.

To understand the biology of our drug targets in both health and disease, we use cultured cells and cells freshly grown from humanely killed rodents. We may also use living cells derived from human volunteers (either healthy individuals or patients with neurodegenerative disease).

We use tissue samples from humanely killed rodents and from human volunteers (either healthy or with neurodegenerative disease) to look at how neurodegenerative disease causes changes to brain tissue.

Computer modelling allows us to predict how drugs interact with their targets and also how they may interact with other proteins in the body.

Why were they not suitable?

These approaches are suitable for much of the work that we carry out. However, in order to fully evaluate novel drugs and their targets, which may have the potential to progress to studies in human volunteers, it is necessary to gain a thorough understanding of how they behave in a whole animal.

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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?

This number is based on estimates of:

- the number of projects that we anticipate running
- the expected number of studies to validate and test potential drugs for each project
- the number of animals needed per study, using the minimum number of animals to give a statistically valid result

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

In designing experiments there are several factors that we will use to reduce unwanted variability in our data. This will reduce the number of animals needed to show that a result is not just due to chance:

- The number of animals used per treatment group will be carefully worked out using data from previous studies to carry out these calculations.
- Randomisation when assigning animals to treatment groups to avoid unwanted bias from factors like cage differences and time of treatment.
- When appropriate, use of baseline data when assigning animals to treatment groups to ensure that baseline measurements between groups do not differ.
- We have many years of experience in study design and statistics within our group and in addition we will draw on support from colleagues who are specialists in biostatistics.

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

Other steps we will take to reduce the number of animals used in our project:

- Where possible, we will use wildtype animals for our studies. This avoid having to breed large colonies of mice, some of which we may be unable to use because they have the wrong genotype.

- Using animals from the same colonies, or if possible, the same litters for comparison, to ensure that genetic variation between animals is kept to a minimum.
- Preliminary experiments in small numbers of animals will be used to determine the optimal conditions for experiments, e.g. the appropriate dose levels of drugs, the length of treatment time, the age at which experiments should be started in mice.
- Where possible, the same individual will carry out procedures, collect and analyse the data within a single experiment. This will avoid variability in data due to differences in how individuals handle and make observations on the animals.
- Where possible, the person collecting and analysing the data will not be told the treatments that have been given to different animals. This is to avoid any bias in the results due to the expected outcome of the experiment.
- Wherever possible we will collect multiple samples from each experiment to avoid unnecessary repetition of studies, these include taking samples to determine drug efficacy, measure drug levels within tissues and investigate possible side effects all from the same experiment.
- Where possible, we will share information, biological samples and mouse strains with other researchers in the field.
- Increased use of cell-based assays and pilot studies, carried out through outsourcing to contract research organisations (CROs) has allowed us to reduce the number of drug targets to validate, and the number of drug-like molecules used in tests. This has allowed us to reduce the number of animals that need to be used for invasive procedures (e.g. procedures that involve dosing, blood sampling or surgery) as opposed to animals whose only procedures involve breeding with genetic modifications.

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.

Wherever possible, wild type mice will be used in studies.

When genetically altered mice are used we will take steps to avoid harm to these animals:

- In some cases, the genetic alteration can be "switched on" by giving a drug either by injection or in the food. This ensures that any harm resulting from the genetic modification is experienced only during the experiment, rather than for the lifetime of the animal.

- Genetically altered mouse models of disease show a progressive worsening of symptoms with age. When using these mice, we will use models with the mildest symptoms and at the earliest ages that are compatible with our scientific objectives.
- When using animals that have been dosed with a substance to induce disease, we will carry out pilot studies to determine the minimum doses and length of time necessary for treatment that are compatible with our scientific aims.
- Surgery to dose a substance directly into the brain will only be carried out if the substance cannot be dosed non-surgically by a different route, and all surgery will be carried out under general anaesthetic using aseptic techniques to minimise the chance of infection. Medication will be given for pain relief.

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

Adult mice will be used in our project. While other, less sentient species, including flies, worms, frogs and fish are commonly used as experimental animals, mice are regarded as a good experimental substitute for humans as much of our genetics, anatomy and physiology are closely replicated in this species. Furthermore, there are existing mouse models of neurodegenerative disease which replicate many of the features of these conditions that are seen in human patients. Adult mice need to be used as the brain does not complete development until adulthood.

Some of our experiments are carried out in anaesthetised animals, and the animal is humanely killed without waking up. However, as we need to observe how drug treatments affect the way animals behave, and the time of treatment usually lasts from several hours up to several weeks, it is usually not possible to keep animals anaesthetised throughout the experiment.

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

Examples of refinement in our experimental procedures include the following:

All mice are acclimatised for at least one week after being brought into the animal facility, before any procedures are carried out to reduce the overall stress experienced by the animal.

Needles used for injections are used only once as they become blunt after multiple uses, causing increased pain and injury.

We use non-aversive handling techniques such as using a cardboard tube to pick up the mice, or supporting their weight with a hand, rather than picking them up unsupported by the tail which is known to cause anxiety.

One of the genetically modified mouse models that we use shows a tendency to be hyperactive and run inside the cage. This behaviour can occasionally cause injury through the bedding becoming tangled around the legs of the animal. We will use a softer bedding type to prevent injury. We will also investigate providing running wheels for these mice. Some of these mice are also substantially smaller than their littermates and the smaller males sometimes suffer bullying from larger mice in the cage. If

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bullying occurs and we need to split cages we try to house the smaller mice together, when possible, to avoid single housing.

In transgenic lines that show disease signs, welfare is regularly monitored and recorded. Toward the end of their lives these animals may experience weight loss, and we use this to monitor welfare. They are weighed at three times least weekly, increasing to daily as the disease signs become clear. Before weight loss reaches 15% of maximum body weight animals are humanely killed.

All surgery is completed using aseptic techniques. Local analgesia is applied and after surgery monitoring in a separate recovery room is also carried out to ensure animals return to normal activity before being transferred back to normal housing. Following surgery and re-housing, they are monitored for activity, weight and wound healing for up to 7 days. This is recorded on welfare monitoring sheets.

In some of our studies, we need to dose a substance using a small pump which is surgically implanted under the skin. We will adopt as standard practice the soaking of these pumps in saline overnight before implantation to reduce adhesion formation on the skin of the animals.

Dosing via the nose is increasingly being recognised as a useful route for dosing substances into the brain. Providing that mice are well habituated to handling and being scruffed and held in a position lying on their back, dosing by this route can be done relatively quickly on conscious animals and avoids the need for surgical procedures to inject substances directly into the brain.

Substances are also delivered via oral gavage - a process requiring a flexible tube through the mouth. The tip of the tube is dipped in a sweet solution before starting the procedure to make it more palatable for the mice to swallow.

When dosing by oral gavage, mice need to be scruffed more firmly than with other techniques to prevent them from biting through the tube. We routinely place the mice on a soft surface, such as a sponge, before scruffing them, as this reduces the possibility of bruising.

When administering drugs in the animals' diet it has been found that the texture and composition of the modified diet is different from the regular diet which the mice usually eat. This has sometimes led to aversion to the modified diet and reduced food, and drug intake. When dosing drugs in the diet, we will acclimatise the mice to the modified diet without the drug for several days before switching to the diet with the drug.

Tamoxifen is a drug that is often used in research to switch on or off the expression of genes in genetically modified mice. This drug causes weight loss which can last for several weeks after dosing has been completed. Animals dosed with tamoxifen are routinely given dietary supplements such as softened food, peanut butter or Nutella to prevent weight loss. Our institutions vets have written guidelines to advise on the best practices for tamoxifen use, which we follow when designing our studies.

Dosed substances usually need to be dissolved or mixed with another substance, known as a vehicle, to make a formulation suitable to administer to the animal. The choice of vehicle is very important as some vehicles can interfere with the experiment by causing unwanted effects. For this reason, in some studies we may also include untreated animals in our studies which are not dosed with a substance but undergo other procedures. While this requires small number of extra animals, this is vital in helping us

to understand the substances we are testing, and to differentiate their effects from those of the vehicle. This will help us to avoid unwanted adverse effects arising from vehicle treatment and to avoid compromised studies caused by interference of the effects of the vehicle with the test substance.

When dosing a substance directly into the brain, surgery is required to allow access via the skull. Surgery, and the act of injecting into the brain may in some cases cause inflammation and damage to the brain tissue around the injection site. For this reason, we may include groups of animals which undergo no surgery, or sham surgery, in which the surgery is carried out but no dose is given. Importantly, this allows us to distinguish between the effects of surgery and the effects of the dosed substance.

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

PREPARE guidelines checklist for designing and planning experiments

ARRIVE guidelines to ensure reporting quality of data is optimised

LASA Guidelines for Aseptic Surgery - https://www.lasa.co.uk/current_publications

NC3Rs - https://www.nc3rs.org.uk/3rs-resources

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

Regular awareness of developments via websites of organisations such as NC3Rs, LASA.

Communications from within our institution and our institution's 3Rs research.

Consultation with named individuals within our institution.