Home Office

NON-TECHNICAL SUMMARY

Development and validation of animal models for neurodevelopmental disorders

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

Key words

No answer provided

Animal types	Life stages
Rats	pregnant, neonate, adult, juvenile, aged

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 project aims to understand how activation of the mother's immune system by viral or bacterial infection during pregnancy can cause of neurodevelopment disorders in the young, principally schizophrenia. From this understanding, we also aim to develop therapies to treat and prevent neurodevelopmental disorders.

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?

Public health science has shown that maternal immune activation (mIA) is an important risk factor for neurodevelopmental disorders (NDDs) in the offspring. These disorders reduce the quality of life for patients and carers. They are poorly treated by existing medication and have a large economic cost burden. Both the pre and post-natal environments are critical for normal development of the fetus and offspring. Our multidisciplinary team has established a rat mIA model, work this application aims to continue. Evidence suggests that mIA, when accompanied by trauma in or around puberty, elevates the risk for later development of NDDs, particularly schizophrenia, above either risk in isolation. In this regard, the 'Second-Hit' appears critical for exaggeration of a pre-existing risk. For this reason we now want to extend our model to include a second hit. An animal model that translates to the human illness will enable new treatments to be developed.

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

Scientific publications, new information for people working to develop better treatments. A validated neurodevelopmental animal model to test new treatments.

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

Scientific publications, new information for people working to develop better treatments. A validated neurodevelopmental animal model to test new treatments.

The scientific community and general public, furthering knowledge, and improving understanding. The pharmaceutical industry, and drug discovery groups, as we will provide new treatment targets. We have close links with the pharmaceutical industry and will inform their drug discovery strategy through these links and via publication of our findings. Patients, carers and the NHS as ultimately this work will lead to new improved medicines for patients.

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

We are committed to publication of positive and negative results, and to public engagement. We have already published our work refining the model and our methods. Several members of the team are experienced in public engagement.

This work started as a collaboration with a large pharmaceutical company, we will continue to collaborate with this sector. We will bring in more collaborators as the project evolves. The team currently consists of experts in behaviour, genetics, placental biology and development. We also engage with psychiatrist experts in this area.

Species and numbers of animals expected to be used

- Rats: 6000

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.

Rats are a popular choice for experimental work because of the detailed existing knowledge of their brain anatomy and behaviour. The rat has been chosen for the present work as much is already known about its cognitive behaviour and the brain functions controlling behaviour. We have extensive experience of studying behaviour in rats. All our current tests and protocols are validated for rats. Rats breed well in captivity and are well suited to longitudinal studies.

To allow us a better understanding of how schizophrenia develops from pre-birth to adulthood we have chosen to study the effects of mIA at critical stages of development. This is, pre-birth, young, adolescent and adult stages in male and female rats.

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

Pregnancy

Pregnant rats may be given a drug treatment regimen by mouth or by injection, or environmental treatment such as enrichment or exercise. This will be done before or after administration of an immune activating agent. A small blood sample will be taken from the tail vein at specified times after this to measure the immune response of the mother. The mothers will be checked regularly for behavioural and physical changes such as changes in grooming, general activity, body temperature and body weight caused by the infection. Some pregnant mothers will be humanely killed to allow collection and analysis of tissue from pregnant females and fetuses. Some pregnant females may be stressed by short term restraint at selected times during pregnancy.

Offspring

Following weaning, behaviour will be analysed in the offspring. The effect of treatments on offspring memory, behaviour and physiology will be investigated. The offspring may be given a drug treatment by mouth or injection, or environmental treatment such as enrichment or exercise. Some offspring will receive an anaesthetic to implant mini pumps for long-term administration of drugs. Some offspring will receive an anaesthetic to record brain activity while unconscious. These animals will be humanely killed at the end of the recording session without waking.

Some groups of offspring will be stressed by mixing up cage groups or short-term social isolation. At the end of the study, or as part of the experimental procedure the rats will be humanely killed.

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

The administration of a maternal immune activator is likely to induce a mild and short-lived infection, slightly increased body temperature or mild sickness in the mother, lasting less than 24 hours. The treatments may cause mild short-term pain from the injection site and also cause mild and short-lived changes in behaviour such as increase/decrease in activity. Stress inducing techniques, such as restraint of the dam, introduction of a male in close proximity to the cage, may be used on some pregnant females and her pups which may cause short-lived, mild changes in behaviour, appearance and general well-being. Behavioural techniques, applied to the offspring, are generally not stressful and can, in certain cases, be considered enrichment for the animals. Some animals will be placed on mild food restriction during behavioural testing and lose no more than 10% of their free feeding body weight. We intend to stress some offspring in adolescence by mixing up cage groups or short-term social isolation. Some rats may undergo anaesthesia for surgery to implant drug delivery pumps under their skin. They recover from this procedure quickly and in most cases no untoward effects are observed. At the end of the study, or as part of the experimental procedure, rats will be killed humanely.

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 maximum severity for both protocols in this license is moderate. Approximately 75% of the animals used will reach moderate severity and 25% of the animals will reach mild severity.

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?

This work is complex and involves understanding the interactions between several body systems. In addition to the changes in the brain function of patients, these disorders are characterised by deficits in social behaviour, memory and mood. Such aspects of NDDs are not possible to model using cells or simulations. This work therefore must entail the use of animals as behaviour is a central feature of the project.

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

None. However we did consider lower order animals such as drosophila.

Why were they not suitable?

Their behaviour and brain and life cycle is too far away from mammalian species to provide a translational model. On consultation with pharmaceutical company colleagues, they considered rodents the most suitable species for this work.

We did not consider non-animal alternatives because there are no non-animal models or systems that replicate the complex interactions and architecture of the central nervous system and the way it communicates with the immune system. If any relevant non-animal alternatives (or less sentient species that are suitable) become
available during the course of the project, we will implement these in our studies. The animal studies will be accompanied by in depth analysis of brain and placenta tissue which may identify a biological marker that could allow us to develop subsequent isolated culture systems to study the pathology of these disorders.

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 is based on data generated from similar studies under the same experimental conditions. We consulted a statistician who advised on the minimum number of animals required to give us the maximum statistical power.

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

We have optimised our statistical analysis through work conducted on our previous licence. We will also use the NC3R's Experimental Design Assistant.

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 follow efficient breeding protocols in consultation with experts, carry out pilot studies with small numbers of animals and always aim to share tissue with team members and other colleagues.

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 are continually refining our behavioural procedures to enhance animal welfare (using species-relevant tests, minimum food restriction, food rewards). When we started this project, we optimised our methodology through an extensive study in non-pregnant rats. Since then, we have refined our methods.

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

It is not possible to mimic complex interactions outside a living organism. Furthermore, this work must entail the use of animals as behaviour is a central feature of the project. We are unable to measure complex behaviour patterns in immature life stages, animals that are less sentient or that have been terminally anaesthetised.

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

Specific on-going refinements include: reduced use of food restriction for the behavioural tests, increasing use of species-relevant tasks, implementing enrichment such as play pens and tummy tickling. We have also optimised our dosing regimens, handling and dosing techniques in collaboration with experts in rodent handling, including reduced restraint. Where animals will be subjected to potentially painful procedures, we will use suitable pain relief to minimise any pain and suffering.

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

We consult with experts to implement improvements in animal welfare. We have access to the extensive library of NC3Rs resources which includes guidelines, practical information and themed hubs. Links to publications, other online resources, and video and training materials.

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

We are registered to the NC3Rs and subscribe to CRACK IT innovation platform and receive updates on advances through NC3Rs newsletters. We are working with our local NC3Rs manager, on implementing environmental enrichment using play pens.