Private & confidential: *Please be aware that the contents of this form may be made public resulting from the "Freedom of information Act". Personal details will not be released.*

G: NON-TECHNICAL SUMMARY (NTS)

Please attach the Non-technical Summary as generated by your application in ASPeL.

Project Title	Treatment and Pathology of Neurological Diseases
Key Words	Therapy, Inflammation, Brain Tumour, Neurological disease
Expected duration of the project	5 year(s) 0 months

Purpose of the project (as in ASPA section 5C(3))

Purpose	
Yes	(a) basic research;
	(b) translational or applied research with one of the following aims:
Yes	(i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants;
No	(ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants;
No	(iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.
Yes	(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 aims mentioned in paragraph (b);
No	(d) protection of the natural environment in the interests of the health or welfare of man or animals;
No	(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work;
No	(f) higher education or training for the acquisition, maintenance or improvement of vocational skills;
No	(g) forensic inquiries.

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):

The aims of this project are: i) Understanding how blood cells and inflammation interact in normal and diseased brains to assist in treatment development ii) to develop new treatments in mouse models of brain diseases and brain tumours iii) to improve brain delivery methods for gene therapy in large animals in preparation for clinical trials.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?

We already have one drug that we developed in a late stage clinical trial in patients. From aim i) we will improve our understanding of how inflammation and other factors influence the development of neurological diseases ii) We aim to develop new and better treatments for neurological diseases using the knowledge gained in aim I, and bring them to the clinic; in particular lysosomal diseases and brain tumours and iii) to improve brain delivery methods in large animals which can be better applied to patients.

What types and approximate numbers of animals do you expect to use and over what period of time?

We will use mainly mice (12,000 over the five year project with 11,500 used in breeding and 4,000 in experiments) and sheep (60 over the five year project).

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels of severity? What will happen to the animals at the end?

The diseases we are studying are inherited genetic diseases of children so we use a number of mouse models. These mice can replicate the disease seen in humans effectively; however, they can become ill. We will be vigilant to observe such signs and to euthanise them if they do. The severity level of these studies is moderate. Sheep have a brain that is much closer in size to humans and this helps to mimic the scale up problems that typically happen when moving a therapy from a mouse to a human – meaning that clinical trials don't always work as they should. Our aim throughout is to develop new treatments, thus, although some treatment methods can be up to moderate in their delivery, (e.g. injection into the brain); we usually expect to see significant improvements in disease status in both mice and sheep. For both mouse and sheep studies, we will collect tissues for biochemical and histopathological analysis.

Application of the 3Rs

Replacement

State why you need to use animals and why you cannot use non-protected animal alternatives

Replacement

Genetic diseases often affect a number of different organs. We need to assess that the therapies we develop have the ability to cure all of the affected organs, especially the brain, so computer based assays and cell culture cannot predict outcomes. Our therapies are assessed with a variety of outcome measures such as behaviour and tissue sampling which can only be achieved with in vivo experiments.

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

We will use statistical calculations to determine the minimum number of animals required for our studies. We will collect data throughout the lifespan of our animals to generate the maximum amount of data. We will also use imaging techniques which will allow us to monitor animals at different timepoints removing the need to sacrifice animals. By applying these methods it will allow us to reduce the number of animals we use.

Refinement

Explain the choice of animals and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

Refinement

For most of the project we aim to use mouse models of genetic disease as they can carry genetic defects similar to human disease. We aim to use a sheep as their brain is a more similar size to a human than a mouse to help us scale therapies up to humans. Where possible, we attempt to prevent onset of disease, rather than treat once disease phenotype has been seen in order to prevent prevents undue suffering. We will use imaging techniques to monitor effectiveness of treatment without needing to sacrifice the animal. -