NON-TECHNICAL SUMMARY (NTS)

Project Title	Translational pharmacology for drug discovery
Key Words	
Expected duration of the project	5 year(s) 0 months

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

Purpose	
No	(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 burden on patients, carers and society of disorders such as Alzheimer's disease, chronic pain and inflammatory conditions is immense and growing with an increasingly ageing population. Unfortunately, current treatments in all of these areas have substantial limitations in terms of the level of effectiveness provided and/or the undesirable side effects caused. The development of new safe and effective medicines are an important facet of how society approaches such unmet medical need.

The aims of this project are to continue our efforts to help facilitate and optimise the advancement of potential new medicines being developed by other drug discovery scientists (e.g. pharmaceutical & biotechnology companies, academic institutions) for chronic disorders of the brain and inflammation. This will be in the form of providing robust evidence from pre-clinical rodent models of likely therapeutic benefit in the clinic, an indication of the levels of drug in blood required to produce such benefit, and a recommendation for the types of patient and clinical outcome measures most suited to the new treatment. The models and technologies that will be used have been refined over many years and have strong translational relevance to the human condition.

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)?

The pre-clinical evidence produced by this project will help identify the best new drugs for progression into human clinical trials and is expected to reduce the currently high number of failures observed in the clinic. Importantly, the scientific translational approach being taken has previously been successful in advancing several new drugs that have proven to have some clinical benefit in Alzheimer's disease and various chronic pain conditions.

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

Over the 5 years of the proposed licence we estimate that we will use: Rat: 15000 Mouse: 5000 Gerbil: 500

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?

A proportion of the techniques used under this licence are minimally invasive and therefore classified as mild. Some animals may have undergone procedure that will cause some pain and discomfort, but will be kept to the minimum possible and these will be classified as moderate. We anticipate only a small number of animals may show adverse effects and where do so they will be culled.

Application of the 3Rs

Replacement

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

Replacement

A range of chronic disorders are covered by this licence, including cognitive deficits associated with Alzheimer's Disease and a range of painful (e.g. osteoarthritis) and inflammatory conditions (e.g. rheumatoid arthritis) and neuropathic conditions (diabetic neuropathy). These are all conditions where the whole organism (i.e. intact nervous system) is required in order to measure a cognitive or painful response.

No in vitro systems are in existence that can replicate the whole functioning organism.

Reduction

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

Reduction

The number of animals will be kept to the minimum required through good experimental design.

For most experiments, sample sizes have been set using power analysis, generally using a significance level of 5%, a power of 80-90%, to detect a difference between groups of 25%. For most procedures numbers of animals per group will be in the 8-12 range depending on the protocol in use. We will continue to monitor group sizes and modify as appropriate based on their analysis.

Most experiments will involve parallel groups, though in some instances a cross-over design may be used if deemed appropriate.

Substances can be administered using a cross-over design, whereby each animal receives all treatments and acts as its own control e.g. where animals have been surgically prepared for EEG or trained to perform a task such as touch screen. Within animal comparisons, are less variable than between animal comparisons, so this will allow the use of smaller groups of animals, to consistently achieve statistical significance.

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

Choice of species

The majority of experiments carried out under this project licence will be in rats and mice. Rats are widely used to provide data in drug discovery because there is a large body of data describing some of the similarities and differences between rat and human physiology. Mice are sometimes used for example in situations where antibodies optimised for use in humans retain their affinity for the equivalent mechanistic target in mouse but not in rat. We may use genetically modified mice, usually this is because no specific inhibitors for the mechanism of interest have yet to become available for the target in question.

Choice of models

The models described in this licence have been extensively used to identify candidate drug molecules, and are of the lowest severity that will allow decision making data to be obtained and where possible a human correlate exists.

Minimisation of suffering

Telemetry devices maybe implanted to measures physiological parameters such as body temperatures, blood pressure & heat rate, this will minimise the stress that maybe experienced with repeated measures such as rectal probe & tail cuff, eliminates the requirement for restraint/tethering and allows the continuous collection of data without the need for any manipulation. Therefore the benefit of the surgical implantation will improve the overall lifetime experience of the animal compared to repeated procedures.

STZ injection produces neuropathy by evoking typical symptoms of diabetes and therefore, animals will drink more than usual and this will be taken into consideration during the husbandry care. 2 % sucrose is added to the drinking water to help avoid the initial hyperglycaemia, and animals will stay group housed to help maintain body temperatures.

All animals undergoing nerve injury for the induction of neuropathic pain, are placed onto an environmental enrichment protocol, where from arrival day enrichment is changed on a Monday (castle) Wednesday (house) and Friday (tubes), to help reduce the incidents of autotomy.

For all pain protocols, we will continue to encourage the use of spontaneous behaviours/ non-invasive endpoints to reduce pain and suffering experienced by the animal, such as weight bearing, burrowing, paw volume and any other more naturalistic behaviours.