NON-TECHNICAL SUMMARY (NTS)

Project Title	Targeting G protein coupled receptors for the treatment of human disease.
Key Words	G-protein GPCR structure-based rodent
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 supply of tissues samples from rats and mice to help develop potential new medicines that target specialised surface receptors (called G protein coupled receptors, GPCR). These receptors make good targets since they are expressed in nearly every major organ and are known to control a diverse range of physiological responses in human. The goal is to aid the understanding of the expression pattern and functional role of

these receptors so that safe effective drugs can be designed to treat human diseases for which threapeutic options are limited.

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 main benefit of this research will be to identify potential innovative therapies to diseases for which there is no treatment or are a marked improvement on the current treatments. G protein coupled receptors (GPCR) are members of a superfamily of cell surface signalling proteins that are critical to a wide range of physiological processes in the human body. It is estimated that over 40% of currently marketed drugs act on GPCRs. There are estimated to be at least 120 GPCRs that are potential targets for new drug treatments. These GPCRs regulate a diverse range of physiological functions involved in the nervous and endocrine systems for example. Using unique newly developed technology, the 3D structures of GPCRs can be obtained and these receptors can be stabilised. This stabilisation makes it possible to look at how potential new drug treatments bind directly to the receptor and measure the binding kinetics of these treatments. Using all this information it is possible to more precisely target the drugs to the binding sites. This enables us to better design potential new drug treatments to a wider variety of targets and more specific to their targets. This targeting of the treatments should mean the resulting drugs are both more effective and have fewer side effects.

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

Rats 1800 Mice 1800

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?

As we try to identify new novel targets for medical drugs and the drugs themselves, studies conducted under this licence may induce some adverse effects in some of the animals. Typical adverse effects include a changes in appearance, for example ruffled fur or changes in behaviour, for example the animals may become subdued. Other effects may include reduction in body weight and/or reduced eating. The larger proportion of animals used in these studies will, however, not experience any noticeable adverse effects. For the vast majority of animals the severity level will be mild. However, as stated above in some studies the animals may experience some adverse effects but these would only cause the animal a moderate level of distress. At the end of the study, the animals will be humanely killed. After the animals are killed samples of body tissue are sent to laboratories for close examination to give more information about the new novel targets and the effects of the potential new medical drugs.

Application of the 3Rs

Replacement

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

Replacement

Potential new drug treatments are initially screened through in vitro assays (human and rodent (pharmacologically relevant) species)) and those that lack activity will not be progressed further for animal testing. While recombinant assays are vital for identifying potential new drug treatments they only go so far. They lack the full repertoire of cellular components normally present in native cells. Hence it is necessary to have a secondary assay using native cell obtained from animals. For studies where the objective is to isolate

and characterise specific cell types from defined tissues (e.g. backlabelling), there are currently no real alternatives to using animals for the supply of these tissue samples.

Reduction

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

Reduction

Pilot studies will be carried out initially to determine the purity and yield obtained from the cell harvest. Cell number requirements will depend on the assay for which the cells will be employed. Based on these initial pilot studies, required sample sizes can be derived for each part of the study.

One strategy to reduce the number of animal requirements is to adopt a protocol designed to enhance the cell yield: this has been successfully applied for deriving peritoneal macrophages where pre-treatment of Brewer thioglycollate medium increases the cells harvested by 10x. Similar strategies will be considered in these studies.

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

Mice and rats are the best animals to use in this kind of study. Their mammalian bodies are incredibly similar to those of humans in many respects and provide a good way of identifying new potential targets for drug development. Also they provide vital information on how a potential new drug treatment will react inside the human body.

Any new drug treatment that is to be given to animal will have been thoroughly profiled through relevant in vitro / cell based pharmacology assays prior to the study to ensure it demonstrates the right pharmacology and that there is a good chance of further development of this treatment.

Painkillers will be given to the animals when appropriate. Most of the studies undertaken within this licence will have no adverse effects on the animals. Anaesthesia will be employed to minimise pain and discomfort in the animals. Adequate post-operative care with daily monitoring will be implemented to ensure the well being of the animals. We have vast experience in how animals react which allow us to identify the most humane point at which to stop an experiment. We can identify the relatively minor reactions to a potential new drug treatment which we know will get worst over time and therefore stop a study before this happens.