G. Non-Technical Summary (NTS)

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed programme of work clearly using non-technical terms which can be understood by a lay reader. You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary will render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at www.gov.uk/research-and-testing-using-animals.

Word limit; 1000 words

Project Title	Novel targets for anti-epileptic drug design
Key Words	Epilepsy, Neuron, Homeostasis, Excitability
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.

No (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 primary goal of this project is to develop new and improved drugs for the treatment of epilepsy. Epilepsy is a common disorder of the brain that affects approximately 1% of the worldwide population. Importantly, almost one-third of epilepsy patients do not respond to currently available antiepileptic drugs

(AEDs). Furthermore, current antiepileptic drugs can cause severe side effects, significantly impairing the quality of life of patients even when seizures are controlled. Thus there is a clear clinical need for better AEDs. The identification of novel biology will greatly catalyse the development of better AEDs. This project is based on identifying such novel targets, for example a protein termed Pumilio (Pum).

Increasing the level and/or activity of Pum is sufficient to significantly reduce the occurrence and severity of seizures. We have identified a chemical compound that is able to increase expression of Pum. This compound is also effective in reducing seizures. However, the compound is not ideal in terms of its drug-like properties. This project will make a range of compounds related to the original, but that are better at being used by the body and hence more effective in controlling seizures. Following testing in mouse seizure models we will hopefully identify which of the new drugs are the best to take forward for clinical trials in human epilepsy patients.

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)?

At present there are a large number of epilepsy patients that cannot be well treated by existing drugs. For many of these individuals surgery is their only option. However, brain surgery is not without significant risks. Thus, being able to find new ways to control seizures may provide a favourable alternative treatment for these patients. The compounds we develop will likely have good potential to meet this clinical shortfall. These compounds will also find significant use in basic research because they will allow researchers to manipulate neuronal and neuron homeostasis activity to further study how seizures develop and how they impact on the brain.

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

We expect to use 312 mice over the course of this 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?

We will induce seizures in 'normal' wildtype mice by administration of specific chemicals. This will allow us to test how effective our test compounds are in preventing seizures. Induced seizures will be expected to change behaviour: including head nodding, pawing, rearing, falling and rolling. Animals that exhibit the most severe Racine 'stage 5' generalised epileptic seizures will be killed immediately by terminal anaesthesia. All other animals will be killed at the end of the observation period by identical means.

Application of the 3Rs

Replacement

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

Replacement

 Epilepsy is a complex disease that cannot, at present, be modelled by cell culture or *in silico*. Moreover, whilst lower organisms (e.g. *Drosophila*, zebrafish) can be used for epilepsy-related research, the significant differences in CNS structure and functionality mean that these alternatives are complimentary. Thus, it is essential to use mammalian models to better represent the complexity of the human brain.

Reduction

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

Reduction

 For all experiments we will use appropriate power calculations (P = 0.05 at 80%) to minimize the number of animals required to provide appropriate statistical power. We will, additionally, when testing new compounds for anticonvulsive efficacy, run small pilot studies to i) determine appropriate dose to use and ii) ensure no adverse toxicity.

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

 The mouse is a good model for the human brain. Moreover, this has been the animal of choice by most research groups working to understand seizure and identify new AEDs over the last 20 years. Thus, our use of mice will allow better comparison of our data to that of others.

Seizures can result in significant behavioural effects in the animals, as in epilepsy patients. However, as far as we are aware mice are probably not aware of the seizure or suffering, similar to humans. In most cases the seizures are short-lived and the animals do not show obvious signs of pain or discomfort post-seizure. Animal welfare will be continually monitored throughout the project. Seizure exposure will be controlled in all cases to prevent large and persistent convulsions and in those rare cases where these are seen, the experiments will be stopped or drugs given to reduce the seizures. In any surgical procedure animals will be given analgesics (pain killers) after surgery. We will always use the lowest number of animals possible to meet our aims. Wherever possible we will use alternatives, and are already doing work in *Drosophila*, which will reduce the number of mice used.