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)

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	Anorexia and cachexia in ageing and disease
Key Words	Appetite, Cancer, Disease, Anorexia, Cachexia
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;
Yes	(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):

About 50% of cancer patients suffer with loss of appetite (anorexia) and wasting disease (cachexia), which can worsen the chances of a successful outcome. This proportion rises to 80% in terminal cancer patients and is considered as the immediate cause of death in a large proportion of these individuals. However, anorexia and cachexia are associated with a range of other types of disease related to inflammation (e.g. colitis and irritable bowel syndrome) or infection (e.g. influenza or parasitic worms). Furthermore, anorexia can also be aggravated by some of the treatments that are used to combat disease, notably cancer chemotherapy. This project aims to understand what the causes of disease-related anorexia and cachexia are. We believe that parts of the brain which respond to natural toxins found in some foods may be responsible for reductions in appetite, while the causes of wasting may be similar to those experienced with natural ageing.

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)?

Our laboratory is well placed to make a major impact on understanding the brain networks that may be behind anorexia and cachexia, as we have a long-term expertise in similar networks which control appetite under healthy conditions. We therefore have available the necessary models and tools to carry out the research effectively. By separating different mechanisms which modify food intake and body composition, we may be able to develop new interventions to bring benefit to those suffering with disease without affecting normal appetite and tissue metabolism.

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

Although the brain's wiring is complex, it is very similar between humans and mice. This gives us the opportunity to use mice to understand normal and abnormal brain function. In fact, the breeding of genetically-modified mice, in which we can introduce transgenes (changes in the mouse genes or the introduction of the human genes) that control normal physiology, has massively accelerated our understanding and our ability to target diseases with drugs. Our techniques are minimally invasive and we need far fewer experimental animals than in the past in order to progress knowledge. We expect to use around 4400 experimental mice over a 5-year period.

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 transgenic mice we use tend to grow and behave in the same ways as normal mice, both in health and disease. Normality is very important, because if a mouse is strikingly different or behaves abnormally, it is unlikely to be very helpful in understanding physiology. Very often we will need to induce illness in our mice, so that we can model cancer, inflammation or infection. However, we do not want our mice to become too ill, since this would mask the things we are trying to study. Therefore, we are collaborating with experts in each type of disease who are very experienced in studying mouse models. To reduce stress, we like to handle our mice (often daily) in order to get them used to being picked up. This means that, when the time comes for an experiment, we can give them an injection (either under the skin, into a vein or directly into the brain) without them hardly noticing. We can also do a range of physiological tests on the mice, sometimes in their home cages, but often after acclimatising them to other cages. Thus, we might put

them in a scanner to see how much muscle and fat they have, or measure their metabolic rate. Occasionally, we even train our mice to poke their noses into holes to break an infrared beam or to press a little lever, which provides them with a sugar reward. This can tell us whether they have lost their motivation to eat or if they are suffering with anxiety-like symptoms. Invariably, the parameters we measure are much simpler: for example, how much food do they eat or how much do they weigh. Often, we need to do surgery on our mice in order to manipulate how the brain responds to diseases or drugs. In this case, we carry out the surgery with the mice under general anaesthetic, plus we give the mice pain killers and sometimes local anaesthetics, to make sure that they do not feel any pain. The mice recover very rapidly, so they can be returned to their home cages to carry on living as usual. At the end of our experiments, all the mice are killed humanely. We can then harvest tissues post mortem and continue gathering useful information.

Application of the 3Rs

Replacement

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

Replacement

Although it is difficult to study healthy behaviour or disease in anything other than a living mouse, we still find out a lot about brain cells by studying them isolated from the rest of the body. We have to kill the mice humanely, but this allows us to take slices of brain and put them in a dish. We can then record the minute electrical activity of individual brain cells. To enable us to identify the right cells in the complex brain, we have bred transgenic mice in which specific cell types glow fluorescently under our microscopes.

Reduction

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

Reduction

For an individual experiment, data provided from similar studies in the past or from pilot studies, allows us to make precise calculations of the minimum number of animals we will need to provide robust results.

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

With between us, over 75 years of experience working with mice, our lab members have greatly improved the way in which we carry out experiments. One major advance has been the use of remote radiotelemetry. This is where, during surgery, we implant a small radiotransmitter under the skin or in the abdomen of the mouse. Later, these devices allow us to monitor things like body temperature, blood pressure and brain activity, which tells us how the mice are “feeling” without having to disturb them.

We now use transgenic mice to identify, control or record the activity of individual cell types in the brain. This allows us to determine how different cells respond to diseases or drugs and how they communicate with each other, without using the very invasive old techniques. Since we can manipulate the mice while they are still in their home cage, we can record their behaviour, whether they are secreting hormones, or if their metabolism is changed, with minimal disturbance. To do this we breed mice that have so-called "designer receptors" expressed in just a single cell type. The designer receptors lay dormant and the mice behave as usual. But, by then giving the mice a "designer drug" or by shining a light through an optic fibre, we can activate or inhibit selective brain cells, while studying changes in behaviour or physiology. All the time, our techniques are improving and our equipment is miniaturising, so it is now even possible to see and record the activity of specific brain cells in freely moving mice, using tiny camera lenses attached to the mouse's head.