G. NON TECHNICAL SUMMARY (NTS)

Project title: Understanding energy balance in health and disease
Duration of project - years: 5
Duration of project - months: 0

Purpose of the project (as in ASPA Section 5C(3)):
(a) basic research: YES
(b) translational or applied research with one of the following aims:
   (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: YES
   (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: NO

Keywords:
Obesity, metabolism, appetite, cachexia

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

Health and wellbeing is dependent upon an optimal amount of body fat and muscle. Obesity, defined as
an excessive storage of energy as fat, causes significant medical and socioeconomic problems. At the
other end of the energy balance spectrum, cachexia, defined as unregulated breakdown of muscle and
fat, is a clinical problem that reduces survival in patients with malignant and inflammatory disease.

Both conditions have unmet clinical need with meaningful intervention requiring an understanding of the
processes involved.

This project aims to investigate how these disorders of energy balance can result from disruption of the
critical pathways functioning in us all that control how we eat, how we metabolise fuel and how we store
excess energy in our tissues.

The basis of these studies come primarily from studies of human disease, including preliminary findings
from rare genetic forms of obesity, data from clinical intervention studies and also larger population
based genetic studies.
We intend to extend these findings and use animal models to help gain a more mechanistic understanding of how the pathways that have been highlighted can go wrong and result in metabolic problems.

We will also examine how these pathways function in the face of different external stressors such as different ambient temperature and different diets because we know that conditions such as obesity are the result of complex interplay between genes and environment.

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)?
In undertaking these studies, we will generate new scientific knowledge around the role of brain-centred pathways that control body composition. We will gain insights into the as-yet-undetermined causes of a severe wasting syndrome which, to date, acts as a barrier to successful therapy in cancer. We will also study the effects of a number of drugs that are being used in metabolic disease to better understand their site of action. These studies will benefit future interventions, being able to signpost potential strategies for therapeutic regimens with less side effects. Finally, we anticipate that we will expand our understanding of the evolving scientific field of the role of so-called "imprinted genes" and their impact on metabolic disease.

What types and approximate numbers of animals do you expect to use and over what period of time?:
We will use mice. We anticipate the need to use up to 10,000 mice over 5 years

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?:
Most experiments proposed will lead to no discomfort beyond that experienced by any rodent bred in captivity and residing in a modern animal facility. Some animals will experience moderate but transient discomfort when given injections or when having blood samples taken. The injections will often be of naturally occurring hormones, or compounds closely related to them and are needed as a way to stimulate and study the workings of crucial metabolic pathways as giving important information on potential therapeutic uses. A minority of animal will also undergo surgery. This will involve placing small cannula into specific regions of the brain and placing bespoke drug delivery devices under the skin and may undergo moderate, limited discomfort in the immediate perioperative period. However, this will be minimised by administration of pain killers. All animals will be humanely killed at the end of the experiments and tissues taken for further analysis.

Application of the 3Rs
Replacement:
Human metabolic disease is the end result of a complex interaction between multiple external environmental factors and internal hormonal, chemical and neuronal messengers. This cannot be meaningfully replicated in anything other than animal models and although we increasingly use non-vertebrate animals like flies and worms which are of lesser sentience than rodents to help in our study, none have the necessary complexity in organ structure or wider networks to adequately address the scientific questions posed.

However, we continue to replace animals whenever possible and have successfully done so using yeast assay systems and neuronal cell culture lines as alternative methods to animal models. We have also begun studies in fruit fly models and developed a screening method to further study genes relevant to metabolic disease that have been identified in human population genetic studies. These
will provide invaluable data to provide focus in future work and replace the need to undertake such screening in mouse models.

Reduction:
To avoid wastage of animals appropriate background research will be done prior to all experiments. Whenever possible, we will look to work with existing colonies of animals rather than breed new colonies. We allow other trained researchers to work with the colonies in our unit rather than moving mice, reducing the number of mice that are bred and transported. Studies will be appropriately statistically powered prior to commencing. Protocols will be planned with a series of analyses and steps undertaken on a single animal. We aim to balance impact upon an individual animal with scientific output but reason that this approach significantly reduces the number of animals used.

Refinement:

Rodent models allow access to metabolically relevant tissues, like the brain and pancreas, that remain, due to ethical and practical considerations, inaccessible in human studies. Rodents have well defined pathways that both match those in humans and are readily amenable to genetic manipulation. To minimise impact on welfare we will use enriched, size appropriate housing; we will use refined standard methodologies in experiments; we will minimise pain using non-invasive techniques whenever possible and using pain relief as required; we have embedded in study plans both steps for monitoring and early detection of potential side effects and should they be encountered, to enable us to apply early humane end points.

To enable accurate measurement of food intake, sometime mice may be singly housed. During this period, there will be appropriate steps to enrich the environment. Shelters, nest boxes and nesting material will be supplied as standard. Tubes to act as hiding tunnels and shredding toys and wooden chewing toys for animals to gnaw on will also be supplied. When not having food intake actively measured, food will also be hidden in bedding and floor covering to give the animals the opportunity to forage.