G. NON TECHNICAL SUMMARY (NTS)

Project title: Metabolic sensing and energy homeostasis
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, metabolic diseases, brain, neurocircuits

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

Obesity is a disease of brain pathways regulating appetite. These pathways rely on sensing
mechanisms to detect how much energy is available in the body and what kind of nutrients are
available for biological functions. Brain nutrient and energy sensing pathways are poorly characterized,
which hinders our ability to develop safe and efficient drugs to prevent and treat obesity. In this project,
we want to characterize brain pathways sensing proteins that are important in the regulation of energy
balance. We know that dietary proteins promote satiety and leanness, but how the brain detects
proteins and how this detection modulates hunger and satiety is poorly understood. Characterizing
these pathways will increase our knowledge of brain pathways regulating appetite and metabolism and
may lead to the discovery of new research avenues to develop safe and efficient drugs in the treatment
of obesity and associated metabolic diseases.

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)?:
Obesity represents a major threat to public health, as it is a major risk factor for premature mortality from cardiovascular diseases and certain cancers. The direct costs of treating overweight and obese people are constantly increasing (£4.2 billion in 2007) while indirect costs reached £27 billion in 2015. There is currently no safe and efficient drug therapy to prevent or treat obesity. The aim of this project is to understand how the brain senses proteins and how this sensing regulates appetite to identify new research avenues for safe and efficient anti-obesity drugs. Direct benefits that will likely arise from this work: increased knowledge and understanding of how the brain senses proteins. These findings will be used by our group and other researchers to further study the biology of brain protein sensing. We will also identify how brain pathways sensing proteins interact with brain pathways sensing energy and other nutrients, to determine if targeting distinct brain pathways in combination could produce greater health benefits. Last, we will determine how brain protein sensing produce a coordinated regulation of appetite and metabolism, to better understand how the body fights against weight loss during chronic energy restriction. Indirect medium-term benefit: Our findings will lay the foundation for follow-up preclinical and clinical research. They will identify candidate therapies directly targeting brain protein sensing mechanisms, pathways integrating protein and energy sensing, and pathways coupling energy expenditure and appetite. We will collaborate with our colleagues at the IMS studying the genetics of obesity in Humans to see if the pathways and genes we have identified are associated with obesity or metabolic diseases in the human population. In the long-term, our findings may contribute to the development of efficient treatments for human obesity.

What types and approximate numbers of animals do you expect to use and over what period of time?:
I expect to use around 6000 wild-type and transgenic 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?:
The majority of animals (90%) are not expected to show signs of adverse effects that impact materially on their general well-being, and may transiently show moderate clinical signs (piloerection, reduced activity). Very rarely the severity of these signs may be such that the humane end points may be reached. Animals are monitored on a regular basis to detect any sign of distress or suffering. Analgesic agents will be administered as required. At the end, all animals will be killed.

Application of the 3Rs
Replacement:

We need to use whole organisms because the control of energy balance and metabolism occurs at the level of the "whole organism" and not simply at a cellular level. We need to use mammals to model how the human brain works because mammals have unique sophisticated pathways to regulate feeding and metabolism. However, we have developed and continue the development and use of primary cell culture, immortalized cell lines and brain explants to model primary sensing mechanisms and intracellular signalling pathways in vitro.

Reduction:

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Refinement:

Rodents allow the study of whole body control of energy balance in a manner relevant to humans, as pathways involved in the control of appetite and body weight are largely similar between rodents and humans. Rodents allow access to several tissues critical to the control of metabolism (brain, pancreas) that are inaccessible in humans. Rodents are amenable to genetic manipulations, offering endless possibilities to characterize mechanisms underlying diseases in a specific and relevant manner.

We will take a number of measures to refine our use of rodents and minimize welfare costs. Animals will be housed according to the best recommendations in a size appropriate environment with shelters and nesting materials. 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. Health and welfare will be assessed daily by competent staffs to detect any upcoming problem at an early stage. By performing pilot studies and choosing well established protocols based on extensive previous experience, we will minimize the unknown effects on the mice and subsequently pain, distress and suffering. We will use non-invasive techniques wherever possible and use pain management when appropriate.