G. NON TECHNICAL SUMMARY (NTS)

Project title: Characterisation of vaccine candidates against viral diseases
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: 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: NO

Keywords:
vaccine, immune correlates, antibodies, cytotoxic T cells, virus

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

The aim of the project is to develop novel vaccine candidates for protection against viral diseases.
Those we are immediately interested in working towards are Ebola, Lassa Fever, Marburg, pandemic
flu as well as seasonal flu and noroviruses.

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)?:
Vaccines have saved millions of lives around the world and continue to offer enormous benefits in
lowering health care costs globally by reducing the morbidity and mortality associated with infectious
disease. However, new and improved vaccines are needed against emerging diseases, as well as
existing infectious diseases for which existing vaccines do not offer 100% protection or where the
protection is only short lived. We expect to be able to identify 1-2 vaccine candidates against severe
viral haemorrhagic fevers that will be taken into clinical trials in collaboration with pharmaceutical
companies.
What types and approximate numbers of animals do you expect to use and over what period of time?:
Adult mice (300 over 5 years) and guinea pigs (750 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 animals are expected to show no adverse effects after vaccination (either by injection or delivery of naked DNA) and testing for immune responses by taking blood samples. However animals infected with disease causing agents may show signs of disease. Vaccinated animals are predicted to be protected by their immune response to the vaccine (this is why they will have been taken infected) but this may prove to be incorrect. The control animals to which we compare vaccinated animals are more likely to show disease signs. Clinical signs may include raised fur and hunched posture, weakness, inactivity, light aversion, and weight loss. These will only be allowed for a maximum of 24 hours before euthanasia. Some animals will be transferred to another project licence for infection should the containment facilities for the disease causing agent used require this and transfers will be in their established groups using climate controlled vehicles. Eventually, all animals with be humanely killed at the end of experiments.

Application of the 3Rs
Replacement:
The induction of the immune responses is complex and has never been recapitulated fully in cells in a laboratory setting, thus animals are required to provide the complex interactions of a whole body system. Animal challenge models are required to establish proof of protection delivered by a potential vaccine before decisions can be made to advance vaccine candidates towards clinical trials in people.

Reduction:
Group sizes are designed to give statistically significant results. Groups are designed to enable comparison between immunised experimental animal groups as well as with ‘mock’ immunised control animals. The mock immunised control groups may be used to compare against more than one experimental group at a time and this ‘sharing’ of control groups means animal numbers can be reduced accordingly. Animals that show appropriate levels of immunity after immunisation can be taken into ‘challenge’ studies. We have linked vaccination studies to challenge studies, to reduce the need for a second set of animals for challenge experiments.

For studies where large volumes of blood are needed to detect antibodies the guinea pig is used rather than the mouse. This is because far fewer animals will be used in consequence to obtain the volume of blood needed for further analysis.

Refinement:

Mice will be used in some immunisation experiments where we want to look at how immune responses to the vaccines are generated. This is because mice have many available reagents to interrogate responding immune cells. This includes both early responses and later adaptive immune responses that may produce antibody. Guineapigs are infectable with several viruses causing disease and provide a larger animal model for testing possible vaccines in which larger volumes of blood can be sampled during immunization schedules allowing different tests to be run with the same sample to measure antibody responses throughout the course of induction of possible protective
immunity. This reduces the number of animals used compared to mice.

Vaccine constructs will be tested in the lab before use in animals. Adverse effects will be minimised by only allowing experimental groups with detectable immune responses to be taken into challenge studies. These animals should therefore be protected from disease or show little/lesser effect from exposure to the disease causing agent. Mock immunised animals may show clinical disease such as raised fur, soft faeces, hunching and weight loss) but as stated above this will be monitored closely and animals humanely killed within 24 hours if the signs continue.