Home Office

Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

The aim of this project is to develop and test next-generation vaccines in a pre-clinical rodent model.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

Why is it important to undertake this work?

Communicable diseases cause a huge health burden each year, contributing substantially to global death and disability. This burden is particularly felt by low and lower-middle-income countries. Indeed, the World Health Organisation (WHO) set out in 2015 in its “From MDGs to SDGs” report (where SDG stands for Sustainable Development Goal and MDG stands for Millennium Development Goal), specifically to focus global attention on ending epidemics such as HIV, tuberculosis, malaria, hepatitis and neglected tropical diseases [1]. Such communicable diseases typically result in morbidity and/or mortality, reducing the years of healthy life as measured by Disability Adjusted Life Years. In addition, such diseases also have a large economic impact, further contributing to global income inequality. The COVID-19 pandemic in particular has highlighted the health and economic impact of communicable diseases.

In the case of malaria, an estimated 409,000 deaths occurred in 2019, down from a previous 736,000 in 2000 [2]. However, due to the increasing prevalence of drug resistance, this progress is under threat. Unfortunately, the case is similar for many other diseases where drugs are used to control symptoms, progression or spread. This includes tuberculosis; one of the leading causes of death worldwide. In the case of tuberculosis, the C£

for broad use. However, this vaccine focuses on one antigen of a highly complex pathogen and as a result, after many years of work, has an efficacy (in the prevention of life-threatening episodes) of approx. 30% [5], much less than the 70% efficacy target. This project aims to use a novel computational approach including multiple antigens to design and test vaccines against such pathogens that have been previously difficult to vaccinate against. Success of the designed vaccines within this project in a pre-clinical model will allow these vaccines to be carried forward externally into clinical testing with the view of reaching the clinic and vaccinating vulnerable individuals.

References

[1] World Health Organisation. (2015). “WHO Health in 2015: From MDGs to SDGs”.

[2] World Health Organisation. (2020). “2020 World Malaria Report”.

[3] World Health Organisation. (2021). “Global tuberculosis report 2021”.

[4] Kim, Y. J., Park, B., & Kang, H. E. (2021). "Control measures to African swine fever outbreak: active response in South Korea, preparation for the future, and cooperation". Journal of veterinary science, 22(1), e13. https://doi.org/10.4142/jvs.2021.22.e13

[5] RTS,S Clinical Trials Partnership. (2015). “Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial”. Lancet. 2015 Jul 4;386(9988):31-45. doi: 10.1016/S0140-6736(15)60721-8. Epub 2015 Apr 23. Erratum in: Lancet. 2015 Jul 4;386(9988):30. PMID: 25913272; PMCID: PMC562600

What outputs do you think you will see at the end of this project?

We expect to see multiple patents filed covering different disease areas. Post vr vMvanv ‘P

- Mice: 2000

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

Explain why you are using these types of animals and your choice of life stages.

Mice will be used in this project due to a number of factors.

1) There are currently no accepted alternative models for vaccinology studies that are both immunologically and physiologically relevant.

2) Mice are a well-established pre-clinical model within the field, allowing reliable extrapolation of data.

Adult mice will be used due to the need for an "average" immune response, which may be affected by age extremes.

Typically, what will be done to an animal used in your project?

Mice will be vaccinated with a prime and a booster dose(s) of the vaccine to be tested via typically intramuscular injection, subcutaneous injection, intravenous injection, or oral gavage. Adjuvants may be used with intramuscular or subcutaneous routes. Blood sampling via the tail vein will occur at key points during immunisation, including pre-immunisation prime and pre-final immunisation boost. Post the final booster dose, mice will be culled for ex vivo (outside of the animal) analysis. A subset of mice will be killed by exsanguination under terminal anaesthesia when analysis of immune cells in the blood is required. Experiments are expected to last two to three months.

What are the expected impacts and/or adverse effects for the animals during your project?

Impact following vaccination prime or boost:

Mice may experience minimal pain from the administration of vaccine lasting in the realm of a few minutes and/or localised swelling at the site of vaccination that could last for several days. Depending on the vaccination platform, i.e. viral vector (commonly adenovirus) vaccines, piloerection may be expected, which would typically be less than 10 days, but may on occasion be prolonged (in excess of 10 days). Where piloerection is prolonged, mice will be culled if they display additional clinical symptoms.

Vaccine adjuvant would be expected to cause transient (under 24 hours) local inflammation only due to use of the"t nf] m1 dmaMdbt_m of t oÛse p thel here"eee adjuvnehb slpxdi ecalh (’hof tfaxi me"eepdi eh (ɔce w

Blood sampling will be limited to small amounts and follow NC3R/LASA standards during the studies to prevent hypovolaemia (i.e. low blood volumes) and taken by a minimally invasive method with hygienic materials to minimise chances of infection.

Why can't you use animals that are less sentient?

Less-sentient animals do not have an immune response that is as representative of the human immune response or as well characterised in the literature.

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?

1) Mice will be group housed where possible to reduce stress and related harm.

2) Environmental enrichment available within the facility will be utilised to reduce stress to the animals.

3) Mice will be monitored regularly post procedure to look for signs of discomfort and distress associated with immunisation at the site of administration as well as behaviour changes.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?

LASA Guiding principles on good practice for Animal Welfare and Ethical Review Bodies.

LASA good practice guidelines - Administration of Substances (Rat, Mouse, Guinea Pig, Rabbit).

LASA good practice guidelines - Handling and Restraint (Rat, Mouse, Guinea Pig, Rabbit)

Use of the website from the NC3Rs (https://www.nc3rs.org.uk) and LASA (Laboratory Animal Science Association) will also be made.

ARRIVE guidelines (Animal Research: Reporting of in vivo experiments).