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NON-TECHNICAL SUMMARY

Development of Novel Epitope-focused Vaccines by Computational Approaches

Project duration

5 years 0 months

Project purpose

- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants
- (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 following aims mentioned in paragraph (b)

Key words

Vaccination, Pre-clinical, Antigen, Communicable diseases

Animal types	Life stages
Mice	adult

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

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 COVID-19 pandemic has regressed progress made in recent years by reducing diagnosis and access to treatment, including specific treatment for drug resistant strains, potentially enhancing drug resistance [3]. In order to tackle such diseases, it is clear that effective vaccination is required. Indeed, vaccination is the only method by which a disease has ever been eradicated; the World Health Organisation declared that smallpox had been eradicated in 1980. By vaccinating individuals, disease severity can be eliminated or greatly reduced, and transmission limited.

In addition to communicable diseases in humans, transmissible veterinary diseases also have a substantial economic and environmental impact. Diseases such as African swine fever; that impacts both domestic and wild pigs, can cause devastation when entire herds of animals must be culled in order to prevent the spread of disease. Current disease control measures include tight biosecurity and import measures in areas unaffected by such diseases, strict sanitation procedures and humane killing of infected animals [4]. An effective vaccine for such diseases would not only alleviate suffering in livestock, but also likely have a positive economic effect, particularly in low and lower-middle-income countries.

Unfortunately, to date, many vaccines have failed or under-achieved due to pathogen complexity or the rate of pathogen mutation. Taking the case of malaria, the vaccine RTS,S has recently been licensed

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 patent filing, we further expect to publish the data in scientific publications.

Who or what will benefit from these outputs, and how?

The benefit of having patented vaccines is the ability to move these forward as vaccines that have the potential to diminish the global disease burden. These vaccines will be taken forward by larger pharmaceutical companies into clinical trials through partnerships with the aim to "bring to market" effective vaccines where previous vaccine strategies have failed. These outputs will be highly modular; we expect to develop multiple vaccines in parallel to patent with each taking under a year, following which they will be partnered. As a result, this will be an output-heavy project.

How will you look to maximise the outputs of this work?

Pharmaceutical partners have already been identified and/or established to take forward the patented work produced in this project. This aids efficient progression of vaccine development.

Species and numbers of animals expected to be used

- 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 most refined options. In the case of some more potent adjuvants such as incomplete Freund’s (the highly potent complete Freunds will not be used), a granulomatous lump (a small area of inflammation) may occur at the site of immunisation. On such occasions animals will be monitored following immunisation and any animals showing signs of distress such as prolonged abnormal behaviour or ulceration that breaks the skin will be culled.

Expected severity categories and the proportion of animals in each category, per species.

What are the expected severities and the proportion of animals in each category (per animal type)?

Expected severity = moderate. Proportion of animals expected to experience this severity = 10%.

What will happen to animals at the end of this project?

- Killed

Replacement

State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.

Why do you need to use animals to achieve the aim of your project?

The immune system is highly complex and is yet to be fully understood. As such, a non-animal alternative is inadequate in identifying the efficacy or immunogenicity of a vaccine. However, prior to immunisation in vivo, expression of the vaccine antigen will be assessed in in vitro culture, ensuring only the most appropriate vaccine candidates are taken forward to in vivo experiments.

Which non-animal alternatives did you consider for use in this project?

Use of organ-on-a-chip technologies or organoid systems (artificial organ).

Why were they not suitable?

Neither of these technologies currently adequately reflect the immune response. Indeed, the immune system and thus response is truly systemic; capturing/mimicking the environment of one organ will fail to reflect the true process of an immune response.

Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.

How have you estimated the numbers of animals you will use?

This estimation is based on a 5 year project, testing 6 vaccines a year with multiple iterations. Each vaccination will be tested in triplicate and including naive control mice as is expected in the literature.

Due to our experience testing pre-clinical vaccines in a mouse model, we are able to carefully plan experiments, minimising the number of mice required. This is aided by careful consideration of appropriate controls and avoiding unnecessary experimental repetition.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

The number of mice required in each experiment will be determined by careful consideration of the literature, our previous experimental experience and appropriate statistics. Each experiment is planned in triplicate as expected in the literature, however data from the first preliminary experiment will be analysed prior to undertaking the biological repeats to determine whether the full experiment is justifiable.

We have used and will continue to use the NC3R's experimental Design Assistant in our experimental planning.

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?

Data from the first preliminary experiment will be analysed prior to undertaking the biological repeats to determine whether the full experiment is justifiable and for power calculations.

We shall also endeavour to share tissue of naïve control animals where this is possible.

Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

We will use a mouse model to test the designed vaccination strategies.

In the immunisation of mice, the most appropriate adjuvant will be carefully chosen in each case for its immunostimulatory action and to minimise the chances of prolonged inflammation or adverse effects in mice. Appropriate choice of adjuvant has the potential to optimise the immune response to immunisation, resulting in a more robust immune response, thus reducing the number of mice required in the study.

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).

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?

We endeavour to stay up to date with the latest literature regarding the 3Rs. We shall work with the Central Biomedical Services and AWERB to ensure that we are aware of the latest developments and implementations. We shall ensure that PIL holders take up the latest training available.