Innovate UK

Results of Competition: Pre-clinical Vaccines SBRI Phase 2

Competition Code: 1806_SBRI_PC_VACCINES_P2

Total available funding is £15 million

Note: These proposals have succeeded in the assessment stage of this competition. All are subject to grant offer and conditions being met.

Participant organisation names	Project title	Proposed project costs	Proposed project grant
National Institute for Biological Standards and Control	Serological Vaccine Standards for Emerging Diseases	£1,999,053	£1,999,053

Note: you can see all Innovate UK-funded projects here https://www.gov.uk/government/publications/innovate-uk-funded-projects
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Project description - provided by applicants
The development of safe, effective and economically affordable vaccines against Emerging Diseases, such as Ebola and Zika, would provide powerful tools not only to prevent re-emergence of these diseases in countries where they are endemic, but also enable swift and effective control of outbreaks initiated by infected returning travellers. However, these infectious agents can only be handled under high levels of bio-security, making the cost of research on these agents prohibitive for most commercial organisations. The availability of established standards and reference materials accelerates the development of licenced vaccines. Where there is robust evidence that convalescent serum (ie serum obtained from someone who has recovered from an infectious disease) protects against reinfection, then the preparation and distribution of serum standards that have been demonstrated to confer protection against infection is hugely beneficial. These serum standards facilitate pre-clinical and early clinical development and selection of the most promising experimental vaccine without the need for expensive studies under bio-containment, as the serum standard provides as in vitro reference marker for serological protection. NIBSC is the global leader in the development of World Health Organisation (WHO) established International Standards and reference materials for biological medicines such as vaccines. At the request of the WHO, NIBSC is undertaking a programme to develop and establish sero-diagnostic reference materials for the WHO's List of Priority Pathogens,that heavily overlaps with the UK Vaccine Network Priority Emerging Diseases. NIBSC has prepared an International Standard for anti-Ebola virus antibodies that was established by the WHO's Expert Committee for Biological Standardisation in October 2017. An anti-Zika virus antibody standard will be reviewed in October 2018 as well as a preliminary report about an anti-MERS-CoV antibody material. Whilst these candidate materials have been through detailed in vitro analyses in international collaborative studies, without additional competitively awarded funding from InnovateUK, it would not have been possible to establish that the serological reference materials contained specific antibodies capable of preventing infection or disease in in vivo model systems. They are now established as serological vaccine standards and available globally. This previous Innovate UK funding, (for 1 year) enabled NIBSC to collaborate with Dstl and PHE laboratories at Porton Down. Their high level bio-containment facilities allowed these critical protection studies to be performed and demonstrated that serological reference materials against Ebola, Zika and MersCoV could protect against these lethal diseases. Having established an effective collaboration between the 3 centres, NIBSC is now seeking a further 2 years funding to build on this momentum, utilising this PLATFORM TECHNOLOGY to prepare a further 9 candidate sero-diagnostic reference preparations, one each for the remaining UK Vaccine Network Priority Emerging Diseases, and establish whether these materials can protect in appropriate in vivo model systems. If materials protect, then they add to the list of serological vaccine standards and thus accelerate vaccine development against Chikungunya, CCHF, Marburg, Lassa Fever, Nipah, Hanta, Rift Valley Fever viruses and bacterial infections Q Fever and Plague.

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Jenner Institute, University of Oxford	CCHF Vaccine manufacturing and First in Human Clinical Trial	£1,999,524	£1,999,524

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Project description - provided by applicants
Crimean Congo Haemorraghic Fever virus (CCHFv) is a severe haemorraghic tick-borne disease which causes outbreaks with a case fatality rate of 10-40%. Ticks infect livestock, mainly sheep, although many species may be infected, and humans may be infected by tick bites or contact with infected animal body fluids after which human to human transmission may occur. The disease is endemic in Africa, the Balkans, the Middle East and parts of Asia and no vaccine is available for either humans or livestock. The Jenner Institute has developed the replication-deficient simian adenoviral vector platform ChAdOx1and ChAdOx2 to produce vaccines against a number of outbreak pathogens. ChAdOx-vectored vaccines are highly immunogenic for both humoral and cell-mediated responses after a single dose, can be produced in a highly efficient manufacturing process and can be thermostabilised. Efficacy in livestock against Rift Valley Fever virus and safety in humans in a number of different vaccine programmes has been demonstrated. A ChAdOx2 CCHF vaccine has been produced and is completely protective in a mouse CCHF disease model after a single dose of the vaccine. We now propose to use established vaccine manufacturing technology to produce a cGMP batch of ChAdOx2 CCHF and conduct a First in Human clinical trial. These are the next steps required for clinical development and eventual licensure and use of a safe, effective, single dose vaccine against CCHF.

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Jenner Institute, University of Oxford	Clinical Stage multivalent vaccines against viral haemorrhagic fevers	£1,999,320	£1,999,320

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Project description - provided by applicants
Since the 2013-2016 Ebola virus (Zaire Ebolavirus/EBOZ) outbreak, there have been a number of other documented outbreaks of lethal haemorrhagic fever caused by filoviruses and arenaviruses. It is generally accepted that either a mixture of monovalent vaccines or, preferably, a multivalent vaccine, will be required to confer protective immunity against viral haemorrhagic fever. The costs of developing individual vaccines against filoviruses and an arenavirus (Lassa virus (LASV)) will be prohibitively high, and there is a risk that funding will not be found to develop individual vaccines, leaving the populations in low and middle income countries at risk. Our vaccine modality of choice, for vaccine manufacture, is a chimpanzee adenoviral vector (ChAdOx1). ChAds have been administered in clinical trials to over 6,500 vaccinees, across eight disease areas, with an excellent safety profile in adults, children and babies. Single dose regimens are highly immunogenic, generating humoral and cellular immunity. Importantly, these vaccines can be thermostabilised by a simple process, removing the need for a cold chain storage and greatly reducing delivery costs. Of note, the emergency response to Ebola led to large-scale manufacture of viral vectors and there is now an accumulated manufacturing experience for viral vectored vaccines at scale. To reduce the costs and increase the utility of vaccines against emerging pathogens, we took a stepwise and iterative approach, in our stream I funding, toward the design and testing of multivalent vaccines against key outbreak pathogens; filoviruses (EBOZ, SUDV, MARV) and LASV. By the end of our programme we had developed, tested and produced scalable, immunogenic, and protective multivalent viral vectored vaccines for deployment against Filoviruses and Lassa fever. We now aim to rapidly translate these promising preclinical vaccines into clinical trials. This is facilitated by the close ties to an in-house bio-manufacturing facility (CBF), an experienced team of personnel at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), adept at progressing first-in-human clinical trials and collaborations in-situ in Africa to clinically assess candidate vaccines in relevant settings. We seek to build on this experience and progress our early pre-clinical work to clinical development and to test a multivalent viral vectored vaccine in a first-in-human Phase I clinical trial.

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
University of Cambridge	Clinical trial of a DIOS Trivalent Haemorrhagic Fever Vaccine (DIOS-HFVac3)	£1,999,926	£1,999,926

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Project description - provided by applicants
Bringing together cutting edge technologies, we have generated a new vaccine candidate that protects against 3 highly contagious African Haemorrhagic Fever Viruses (HFV), which have significant global epidemic potential. With this technology, we can achieve dramatic improvements to the breadth of protection conferred by vaccines against emerging and re-emerging pathogens. Our DIOS (Digitally designed, Immune Optimised and Selected) technology provides the broadest possible protection against viral variants to limit future outbreaks of highly variable pathogens. In our Innovate Stage 1 project, we achieved clear proof-of-concept for this platform, moving quickly from demonstrating DIOS platform immunogenicity to generate a unique trivalent vaccine candidate. In a second Stage 1 project, animals vaccinated against three diverse viruses - Lassa, Ebola and Marburg were protected from lethal infection. Our top candidate next generation DIOS antigens, targeting these 3 diverse families of HFVs, gave the broadest immune responses and proved stable in the MVA vaccine vector. In the Innovate Stage 2 project we propose to take this to next stage, performing a “first-in-human” clinical trial of DIOS vaccine inserts to demonstrate the safety profile of the DIOS-HFVac3 candidate and its improved breadth of the immune responses in human volunteers. We have proven that DIOS inserts based on both the DNA vaccine vector pEVAC and the highly immunogenic poxvirus vaccine vector, Modified Vaccinia Ankara (MVA), provide protection from infection. MVA is a safe vector that was used to successfully immunise against smallpox. It is well characterised and has further been modified as a versatile vaccine vector for many pathogens. MVA additionally provides 100% vaccine efficacy against Monkeypox, a disease which is currently causing outbreaks in humans in the same regions where DIOS-HFVac3 would be deployed as a vaccine. It has been demonstrated that cold chain independent vaccine lots of MVA can be produced and we would aim to achieve this with both the pEVAC and MVA DIOS inserts for rapid deployment wherever outbreaks may occur. Our human clinical trial design will have two arms, one with MVA/DIOS-HFVac3 alone, and the other with co-administration of MVA expressing a fourth HFV found in Africa, namely Crimean-Congo Haemorrhagic fever virus (CCHFV). In collaboration with the MVA-CCHF Innovate clinical trial consortium, GMP lots of MVA-CCHF, made to the same standards as MVA-DIOS-HFVac3, will be used for co-administration. This represents a unique opportunity to evaluate if a tetravalent human VHF vaccine will provide equivalent immunogenicity, and potentially protect humans against 4 VHF pathogens (Lassa, Ebola, Marburg, CCHF) as well as Monkeypox. 5. Description of Proposed Idea/Technology

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Imperial College London	EML-VAC: Multivalent replicon vaccine against Ebola, Marburg and Lassa viruses	£1,999,713	£1,999,713

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Project description - provided by applicants
A multivalent haemorrhagic fever vaccine based on synthetic replicating ribonucleic acid would provide one of the fastest and most cost-effective approaches to stop viral outbreaks at their source. This affords significant advantages over more conventional vaccine approaches such as viral vectors, and attenuated pathogens and would be safer in individuals unable to receive live attenuated vaccines (e.g. children and the immunocompromised). Our program aims to develop a multivalent vaccine against the most common human viral haemorrhagic fevers (Ebola, Marburg and Lassa fever virus). The choice of targets is based on strong scientific evidence that gene-based approaches can protect against infection in preclinical models. This vaccine may also find utility as a booster that can be used in combination with existing vaccines (e.g. rVSV-EBOV). The fully synthetic manufacture and ease of production provides the potential to produce hundreds of thousands of doses within a matter of weeks where the individual vaccine components targeting different haemorrhagic viruses can easily be combined. This may be critical to the global response against emerging haemorrhagic viral infections, as the nature of the next outbreak cannot be reliably predicted. In this respect the proposed multivalent vaccine has potential not only to protect against multiple known haemorrhagic viruses but is also more likely to show cross-protection against novel variants that may arise in the future. In Part 1 of this project (now complete) we successfully completed the heavy lifting required to move our RNA platform from a research process through to fully established robust and validated manufacturing process, confirming the potency of the produced product in preclinical models. In this Part 2 project we will manufacture clinical grade material (GMP), conduct the required preclinical toxicology and early evaluation of the vaccine in a phase I human clinical trial designed to assess the safety and immunogenicity of our pan-haemorrhagic fever vaccine. Our ability to deliver on the aggressive timelines required to move from manufacture through to completion of a first in human clinical trial within two-year grant funding period is only possible due to the robustness and speed of our manufacturing process and the unique competency of the assembled team in translating vaccine concepts from the bench to the bedside . Ultimately our vision is to use our vaccine platform to ensure UK preparedness for any eventual pandemic and to make vaccines globally available in the event of any outbreak situation. Our approach will ensure appropriate costing for low and middle-income countries and be readily available to organizations focused on global health (e.g. MSF and WHO): these groups have historically been the first to detect, and/or respond to an outbreak, and are therefore ideally positioned to assist in implementing any vaccination strategy. Our Target Product Profile (TPP) is a stable multivalent vaccine that can elicit protective immunity against the most common human viral haemorrhagic fevers following one or two immunisation across all populations, has potential for boosting in the absence of anti-vector immunity, and can be rapidly manufactured at low cost.

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Public Health England	Advancement of a cost-effective MVA-based Hantavirus vaccine (HantaVacc).	£2,000,000	£2,000,000

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Project description - provided by applicants
Seoul virus (SEOV) and Hantaan virus (HTNV) are widespread pathogens maintained in rodents and transmitted to humans in aerosols of rodent excreta. Human infection results in Haemorrhagic Fever with Renal Syndrome (HFRS), a key burden of disease in many low and middle income countries with between 100,000-150,000 cases documented worldwide per year. Whilst other Hantaviruses exist, they cause more infrequent types of disease or are geographically restricted to the Americas, the need for vaccine intervention against them is less urgent than for SEOV and HTNV. During the 12 month Stream 1 funded project, we developed a multi-valent vaccine, termed MVA-HantaVacc, based on the vector Modified Vaccinia Ankara (MVA) containing a recombinant mosaic nucleoprotein of SEOV and HTNV. MVA-based vaccines are efficient and cost-effective; they offer many advantages including a proven safety record, the ability to elicit both cellular and humoral immunity, thermostability and ease of manufacture. We then demonstrated that MVA-HantaVacc is immunogenic in mice. A strong antigen-specific recall T-cell response was observed along with production of Hantavirus-specific antibodies. In the absence of a suitable laboratory disease model of SEOV or HTNV infection, vaccine efficacy was assessed in type-I interferon receptor knockout mice (strain A129) which can be experimentally infected with SEOV. Animals immunised with MVA-HantaVacc demonstrated clearance of virus from key tissues in contrast to control groups. This is the first demonstration of a successful research grade MVA Hantavirus vaccine. In order to further progress MVA-HantaVacc through a Phase I human clinical trial, we will first re-engineer the Hantavirus nucleoprotein antigens into a GMP-compliant MVA vector. We will then demonstrate bioequivalence of the new vaccine with the 'research grade' vaccine, before manufacturing a GMP batch which will undergo stringent quality control and toxicity testing. Once complete, MVA-HantaVacc will enter into a Phase I clinical trial to test safety and immunogenicity in healthy human volunteers. We have already started discussi

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University of Oxford	Development of a novel vaccine to protect against Q fever epidemics: late stage preclinical formulation and progression to clinical trial	£1,054,907	£1,054,907

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Project description - provided by applicants
Development of a novel vaccine to protect against Q fever epidemics: late stage preclinical formulation and progression to clinical trial. This project aims to progress a novel vaccine against Q fever (Coxiella burnetii), developed during an Innovate UK stream 1 project, to clinical development, by identifying the minimal formulation required for protection, and includes production of the pre-GMP starting material in an approved GMP production facility. Our novel vaccine against Q fever uses a potent vaccine delivery technology suitable for outbreak situations in low-income countries. Q fever is a highly contagious bacterial disease, currently regarded as a global health concern and a potential outbreak pathogens by the UK government, the CDC and WHO for several reasons: 1. It causes a range of disease from acute to potentially fatal chronic infection. 2. Extensive and costly antibiotic use may be required during outbreaks. 3. Chronic Q fever is very difficult to treat. 4. The symptoms are non-specific and thus Q fever is difficult to diagnose. 5. Q fever has a worldwide distribution, particularly affecting low-income countries. The number of reported cases is likely an underestimation. A large epidemic occurred recently in the Netherlands (2007 to 2010) that led to several deaths and long-term illnesses. 6. The bacterium is unusually resistant to drying and to heat, it can survive for years, and extremely low infectious doses (down to a single bacterium) are sufficient to cause infection. It is therefore also a potential bioweapon. The inactivated whole cell vaccine licensed in Australia induces severe adverse effects, particularly in pre-exposed individuals (a phenomenon known as sensitization), and thus requires pre-vaccination screening, not suitable for extensive use particularly in low-income countries and for outbreaks. The protective efficacy of conventional vaccines based on proteins in adjuvant is very limited, in part due to the weakness of this formulation in inducing the cellular immune responses that have been linked to resolution of Q fever infection. Our novel vaccine is based on the judicious use of a highly immunogenic replication-incompetent viral vector, able to induce the desired T-cell responses without the side effects of the whole cell vaccine. The viral vaccine technology is currently used for developing new vaccines against several infectious diseases such as Ebola, malaria, influenza, HIV, TB, capsular group B meningococcus and plague. It is particularly suitable for diseases for which cellular immune responses are required for protection, as is the case for Q fever. We have created vectored Q fever vaccine candidates, and demonstrated that a single dose injection of three or five components induces strong T-cell immune responses. A combination of three antigens was able to reduce Q fever infection in a mouse model. In this follow on project, we will identify the minimal protective antigen composition responsible for the reduction of infection, design and produce the clinically relevant vector suitable for human use. The pre-GMP (good manufacturing practice) starting material will then be produced, ready for GMP production and phase I trial. Our group has expertise in progressing vectored based vaccines against bacterial pathogens to GMP production and phase I trial.

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