Appendix 2.2: Track-record – Four cases EVI

(1) Malaria vaccines based on innovative viral vectors

Background:
Malaria caused by *Plasmodium falciparum* results in the deaths of more than half a million people every year. The majority of deaths occur in children living in sub-Saharan Africa. While methods such as the use of anti-malarial drugs, and insecticide-treated bed-nets exist for malaria control, there are no effective vaccines licensed to date. A vaccine giving strong and lasting protection would provide the most cost-effective and long-term solution for the prevention of this deadly disease.

In the Malaria Vectored Vaccines Consortium (MVVC) project, the further clinical testing of a novel a prime-boost vaccine regimen was undertaken that was based on innovative viral vectors (chimpanzee adenoviral vector, ChAd63; and Modified Vaccinia Ankara virus, MVA) encoding the ME-TRAP malaria antigens. The study was undertaken in different study groups of (adults, young children, infants) in various countries in East and Western sub- Saharan Africa.

Objectives:
The overall objective of MVVC was to further develop a safe, non-reactogenic, effective and affordable malaria vaccine for use by the malaria-endemic populations, and to undertake the clinical research within a workplan that integrated important capacity strengthening activities at the African partner sites.

The specific objectives were:

- To conduct phase I and II clinical trials of the vaccine candidates in adults, children, and infants in East and West Africa to assess the efficacy, safety and immunogenicity of this novel prime-boost regime
- To ensure continued maintenance and further consolidation of the well-established clinicial research capacities at the different African partner sites and to facilitate the upgrading of the less-established sites
- To develop clinical trial capabilities, infrastructure and human resources that ensure the sustainability of the investigational sites beyond the end of the project.

Project partners:

- European Vaccine Initiative (EVI) (coordinator), Germany
- University of Oxford (UOXF), UK
- Okairòs s.r.l., Italy
- Centre National de Recherche et Formation sur le Paludisme (CNRFP), Burkina Faso
- Kenya Medical Research Institute (KEMRI), Kenya
- Medical Research Council Gambia (MRC), The Gambia
- Université Cheikh Anta Diop (UCAD), Senegal
- Vienna School of Clinical Research (VSCR), Austria
- Various academic organisations and small- and medium sized entreprises as subcontracted service providers.

Funders:

- European and Developing Countries Clinical Trials Partnership (EDCTP)
- Irish Aid, Department of Foreign Affairs and Trade, Ireland
- Swedish International Development Cooperation Agency (Sida), Sweden
- Medical Research Council (MRC UK), UK
- Federal Ministry of Science and Research, Austria.

Project duration and total budget:

- 2009-2015; € 10,644,000

Major achievements and results:

- The prime-boost vaccine combination using ChAd63 ME-TRAP and MVA ME-TRAP was shown to be safe and immunogenic
- The infrastructure and laboratory equipment upgrade was completed at the CNRFP site in Banfora (Burkina Faso) and at the UCAD research site in Keur Socé (Senegal)
- An extensive training progamme was implemented, including the training of MSc and PhD students, and postdoctoral research fellows, as well as many short-term trainings
- Several researcher exchange visits took place to reinforce collaborations, especially between the African project partners
- Workshops were organised for students and administrative staff focusing on areas such as basic and applying Good Clinical Practice, data management and protocol development
- Major results of the MVVC studies were published in peer-reviewed journals
- Transparency and accountability was ensured by effective financial management, including financial audits that were undertaken.

Sustainability:

- Follow-up funding to MVVC for an additional 3 years could be secured that allowed the further testing of the ChAd63 and MVA-based vaccine candidates, as well as of an additional malaria vaccine candidate. **NB:** The additional malaria vaccine candidate included in the follow-up study was R21, the malaria vaccine candidate included in the present application to the Dutch MFA.
- The ChAd vector technology co-developed by UOXF that was tested in MVVC is underlying the Oxford–AstraZeneca COVID-19 vaccine, approved by several regulatory agencies worldwide, including the European Medicines Agency (EMA) and others
- The capacity strengthening activities at the CNRFP and UCAD research sites have strongly contributed to both sites becoming well-developed, efficient, reliable and stable infrastructures that have enabled the formation of a network of European and African partners working together to efficiently conduct the clinical development of vaccines for a range poverty-related neglected diseases.

(2) Placental malaria vaccine candidates

Background:
Placental malaria (PM) is caused by a life-threatening malaria infection during pregnancy and accounts for an estimated 200.000 infant deaths annually, 819.000 children with low birthweight, and is estimated to cause 50.000 maternal deaths each year. PM causes adverse pregnancy outcomes, including anemia and hypertension in first-time pregnant women, and low birth weight due to premature delivery and fetal growth restriction, which are associated with a higher risk of fetal and neonate morbidity and mortality.

A compelling strategy to prevent PM is the development of disease-specific vaccines that could protect both mother and unborn child from morbidity and death from PM, either by being used on their own, or in combination or complementation with other, already existing yet imperfect malaria prevention and treatment tools.

Objectives:
The overall objective of the activities was (1) to obtain the proof of concept that a vaccine based on the leading antigen for this indication (VAR2CSA) can be designed for human use to induce long lasting cross-reactive and inhibitory antibodies; and (2) to undertake the manufacturing and early clinical testing of placental malaria vaccine candidates.

The specific objectives were:

- Generation of different recombinant forms of the VAR2CSA antigen and assess their activity as immunogens that elicit functional and cross-reactive antibodies against placental parasite
- To select the best candidate antigens from the preclinical studies
- GMP manufacture of the PM vaccine
- Conduct of a phase I clinical trial
- Implementation of a field site and preparation of a protocol for a phase II clinical trial in African women
- Strengthening of the clinical trial capacities at the African partner sites, especially at the new trial site that was established at UAC in Benin.

Project partners:

- European Vaccine Initiative (EVI) (coordinator), Germany
- University of Copenhagen (UCPH), Denmark
- Institut national de la santé et de la recherche médicale (Inserm), France
- Centre National de Recherche et Formation sur le Paludisme (CNRFP), Burkina Faso
- Université d'Abomey-Calavi (UAC), Benin
- Institut de Recherche pour le Développement (IRD), France
- University of Tübingen (EKUT), Germany
- National Institute of Allergy and Infectious Diseases (NIAID), USA
- Numerous academic organisations and small- and medium sized enterprises as subcontracted service providers.

Funders:

- German Ministry of Education and Research (BMBF) through Kreditanstalt für Wiederaufbau (KfW)
- Irish Aid, Department of Foreign Affairs and Trade, Ireland
- European Commission (EC), Belgium
- Inserm, France
- Institut national de la transfusion sanguine (INTS), France.

Project duration and total budget:

- 2011-2018; €17,096,000

Major achievements and results:

- Down selection of the best antigens expressed in *E. coli* or insect cells and their transitioning to clinical development.
- Two different adjuvants were compared and the best one selected for further clinical studies in combination with each antigen
- Successful manufacture and release of the GMP vaccine batches
- Successful conduct of staggered, randomised and controlled phase Ia/b clinical trials. Trials were conducted in healthy adult subjects not exposed to malaria in Germany or in France and in exposed subjects living in malaria-endemic regions of sub-Saharan Africa. Vaccines were demonstrated to be well tolerated and immunogenic.
- Major results were published in peer-reviewed journals
- Implementation of a quality assurance system in the new clinical trial site established at UAC in Benin.
- Transparency and accountability were ensured by effective financial management, including financial audits that were undertaken.

Sustainability:

- Follow-up funding for the further clinical testing of the PM vaccines could already be secured from the EC and the Japanese GHIT Fund. **NB:** Further financial support for the more extensive clinical testing of the VAR2CSA-based vaccine candidates, as well as for the clinical testing of the R21 for PM, is being requested via the present application to the Dutch MFA.
- African partners are frequently involved in a range of clinical research activities coordinated by EVI in Africa.

(3) Malaria vaccines that prevent mortality and morbidity: blood-stage malaria vaccines - AMA1-DiCo

Background:
The *Plasmodium* parasite that causes malaria is transmitted to humans through the bite of an infected female *Anopheles* mosquito. Clinical malaria occurs when *Plasmodium* parasites in an infected human invade red blood cells and replicate therein (the so called blood-stage infection).

The parasite has different life stages (pre-erythrocytic, liver, blood and sexual stages). When developing vaccines, different stages of the parasite's life cycle can be targeted. Immunological studies have demonstrated that the immune response induced by blood-stage antigens can protect against the disease. Consequently, blood-stage malaria vaccines represent a promising and complementary approach to pre-erythrocytic vaccines and are considered an important component of a second-generation multi-antigen, multi-stage malaria vaccine.

Objectives:
The overall objective was to assess the clinical safety and immunogenicity of the so-called AMA1-DiCo blood stage antigen. For the malaria parasite, AMA1 (Apical Membrane Antigen 1) is essential for its invasion of human red blood cells. In this particular project, an artificial AMA1 protein version -AMA1-DiCo(Diversity Covering) that was designed and tested that has the potential to overcome the variability of the AMA1 protein found in nature.

The specific objectives were:

- Process development and GMP manufacturing of the AMA1-DiCo vaccine
- Development of a fast-track strategy for the accelerated clinical testing of vaccines
- Conduct of a staggered multi-centre phase Ia/b clinical trial of AMA1 DiCo
- To compare the effect of two different adjuvants when used for the formulation of the AMA1-DiCo vaccine.

Project partners:

- European Vaccine Initiative (EVI) (coordinator), Germany
- Biomedical Primate Research Centre (BPRC), The Netherlands
- Centre National de Recherche et Formation sur le Paludisme (CNRFP), Burkina Faso
- Centre d'investigation clinique Cochin-Pasteur (CIC-Cochin), France.
- Institut national de la santé et de la recherche médicale (Inserm), France
- Other academic organisations and small- and medium sized enterprises as subcontracted service providers.

Funders:

- Ministry of Foreign Affairs, The Netherlands
- Irish Aid, Department of Foreign Affairs and Trade, Ireland.

Project duration and total budget:

- 2008-2017; €6,000,000

Major achievements and results:

- Successful manufacture and release of the GMP vaccine batch
- Successful clinical testing, showing that AMA1-DiCo vaccine candidate was safe and well-tolerated when formulated with either of the two adjuvants tested
- Successful testing of the fast-track clinical trial strategy, offering an important saving of time as compared to the traditional clinical trial strategy (this accelerated fast-track strategy has since then successfully been used by EVI in many other clinical trials)
- Major results were published in peer-reviewed journals
- Transparency and accountability were ensured by effective financial management, including financial audits that were undertaken.

Sustainability:

- The accelerated fast-track strategy developed and tested in this project has since successfully been used by EVI in many other clinical trials in Africa
- Outcome of a recent application to the EC for follow-up funding for the further clinical testing of AMA1 DiCo is currently pending (the grant application had been invited for a stage 2 application; funding decision expected in Jan 2023).

(4) Malaria vaccines that prevent mortality and morbidity: blood-stage malaria vaccines - BK-SE36

Background:
Same as above under "Case study 4 – AMA1-DiCo"

Objectives:
The blood stage antigen SERA5 N terminal domain (SE36) is another promising malaria vaccine candidate. This notion is based on findings obtained via epidemiological studies, *in vitro* studies, as well as studies in non-human primates in which the SE36 vaccine candidate had shown protection against a *P. falciparum* challenge. Overall objective of this project is to further develop and test in human clinical studies a recombinant form of SE36 as blood stage malaria vaccine.

The specific objectives were:

- Conduct of a phase Ib clinical trial in Africa to assess the safety and immunogenicity of the BK-SE36 vaccine candidate in healthy malaria exposed African children
- Generate additional data on safety, immunogenicity to allow comparison of the new clinical trial results with some obtained before in another African country with different malaria endemicity
- Conduct of a follow-up study of Japanese volunteers that participated in the first-in-man phase Ia trial of BK-SE36 vaccine
- Conduct a phase Ib clinical in Africa to assess the improvement of the immune response when the vaccine is formulated with another adjuvant (BK-SE36/CpG) in adults and children
- To evaluate and compare different pre-erythrocytic and blood-stage vaccine candidates for safety, immunogenicity and efficacy in phase II trials, and to identify the most promising candidate(s) for further clinical development in phase III trials
- To strengthen translational vaccine development platform capabilities and reinforce the clinical trial infrastructure/equipment in African sites

Project partners:

- European Vaccine Initiative (EVI) (coordinator), Germany
- Groupe de Recherche Action en Santé (GRAS), Burkina Faso
- Institut de Recherche en Sciences de la Santé (IRSS), Burkina Faso
- Research Institute for Microbial Diseases (RIMD), Japan
- Nobelpharma Co, Ltd, Japan
- London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom
- Centre de Recherches Médicales de Lambaréné (CERMEL), Gabon
- Fundação Manhiça, Mozambique
- Ifakara Health Institute Trust (IHI), Tanzania
- Academisch Ziekenhuis Leiden (LUMC), The Netherlands
- University of Oxford (UOXF), UK
- Eberhard Karls Universität Tübingen (EKUT), Germany
- Luxembourg Institute of Health (LIH), Luxembourg
- Other academic organisations and small- and medium sized enterprises as subcontracted service providers.

Funders:

- Global Health Innovative Technology Fund (GHIT) Fund, Japan
- Nobelpharma Co., Ltd., Japan
- BIKEN Co., Ltd., Japan
- Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan
- Japan Agency for Medical Research and Development (AMED), Japan
- European and Developing Countries Clinical Trials Partnership (EDCTP), The Netherlands
- Irish Aid, Department of Foreign Affairs and Trade, Ireland

Project duration and total budget:

- Since 2014 (still ongoing); €5,695,000

Major achievements and results:

- BK-SE36 vaccine candidate was found safe and immunogenic in African children
- BK-SE36 induce a long last immune response in Japanese volunteers
- BK-SE36 vaccine candidate adjuvanted with CpG induces an improved immune response in young children
- The laboratory equipment was upgraded at GRAS (Burkina faso)
- Major results of the BK-SE36 trials studies were published in peer-reviewed journals.

Sustainability:

- Several rounds of follow-up funding have been obtained since the project start in 2014, including three additional rounds of funding from GHIT and one from EDCTP. The latest funding obtained has the aim to support the conduct of a Phase IIb trial with the manufacture and preclinical testing of a new vaccine batch and related activities, as well as to undertake the comparative testing of different vaccine candidates in humans in the context of a multilateral initiative in Africa.