A Multi-Stage Malaria Vaccine

Rapports

Informations projet

MultiMalVax

N° de convention de subvention: 305282

Projet clôturé

Date de début
1 Octobre 2012

Date de fin
31 Mars 2017

Financé au titre de
Specific Programme "Cooperation": Health

Coût total
€ 8 055 788,47

Contribution de l'UE
€ 6 000 000,00

Coordonné par
THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD
United Kingdom

Ce projet apparaît dans...

Final Report Summary - MULTIMALVAX (A Multi-Stage Malaria Vaccine)

Executive Summary:
4.1.1 Executive summary
A highly effective malaria vaccine should help prevent almost half a million deaths, perhaps more, from malaria each year (1). Since the 1980s over 30 vaccine candidates have entered clinical trials, with several candidates proceeding to phase II efficacy trials, often using the well-established sporozoite challenge model. In recent years, there has been substantial progress in the development of single antigen pre-erythrocytic vaccines that point to the feasibility of developing a high efficacy vaccine that could make a major impact on malaria control. A highly effective malaria vaccine is still a major objective of global health research, and will likely require a multi-stage product. New vaccine technologies and the increasing success of antigen discovery approaches now make accelerated design and development of a highly effective multi-antigen multi-stage subunit vaccine feasible. To this end MultiMalVax undertook first a series of phase I / II clinical trials assessing pre-erythrocytic, blood-stage and mosquito-stage components individually, and then subsequently assessed the most promising vaccines candidates from two different stages in a combination challenge trial.
MultiMalVax is a pan-European project that is addressing shortcomings in the fight against malaria. MultiMalVax partners comprise five European organisations involved in vaccine development, each contributing with specialised expertise and technology. The Jenner Institute at the University of Oxford (UOXF), UK, is an academic institution with key expertise in malaria vaccine development and viral vector delivery systems, and is coordinating the overall project. The European Vaccine Initiative (EVI), DE is assisting with project management tasks and advising on production and the clinical aspects of the project. The third member is the Université Pierre et Marie Curie (UPMC), FR with a strong background and expertise in Plasmodium falciparum pre-erythrocytic in vitro assays. The partners are complemented by the pharmaceutical industry partners GlaxoSmithKline Vaccines (GSK), IT/BE and the small and medium-sized enterprise Reithera srl, IT with expertise in vector development and manufacture. This collaboration of academic and industrial partners together with the major European product development partnership for malaria vaccines provided complementary and highly relevant abilities to accelerate development of this promising product.
The overarching aim of the MultiMalVax clinical development programme was to develop the concept of a highly effective multi-stage malaria vaccine to the point of proof-of-concept phase II efficacy testing in

Europe, prior to field trials in malaria-endemic areas. MultiMalVax will undertake phase I / II clinical trials to assess the pre-erythrocytic, blood-stage and mosquito-stage components individually or together, using state-of-the art immunomonitoring, key functional assays of vaccine-induced immunogenicity, and sporozoite and blood-stage parasite challenges to demonstrate vaccine safety, immunogenicity and efficacy.
Achievements: MultiMalVax successfully completed first-in-human phase I clinical trials for the adjuvanted sporozoite-stage malaria vaccine candidate R21, the blood-stage antigen PfRH5 and the transmission blocking vaccine candidate Pfs25, to complement the already available ME-TRAP vectored liver-stage vaccine candidates. This was completed by combination phase I/II clinical trials assessing GSK's RTS,S administered with vectored ME-TRAP as well as R21 in adjuvant administered with or without vectored ME-TRAP. All approaches have shown favourable safety and immunogenicity profiles and important positive efficacy data was achieved in 2017 with a new vaccine candidate. Progress was also made in the establishment of a functional in vitro assay that allows quantification and further analyses of the immunological responses induced by liver-stage vaccines.
Some of the MultiMalVax scientific achievements have been published in peer reviewed journals and presented at several conferences to the scientific community and general public. The MultiMalVax team will ensure that other more recent results will be made public shortly. For more information about the MultiMalVax project, please visit the website.

Project Context and Objectives:
4.1.2 Project context and objectives

Malaria vaccine development has proved difficult (2) and only a handful of the candidates, all pre-erythrocytic vaccines, have shown statistically significant efficacy in phase II clinical testing. Among the well-recognised difficulties are the following: substantial stage-specificity of gene expression so that antigens from one stage are not protective at another; antigenic variation in a major blood-stage antigen PfEMP1; substantial polymorphism, particularly in blood-stage antigens that are targets of natural immunity; difficulty in expressing antigens in the correct conformation. Finally pre-clinical testing and clinical trials have revealed that, to obtain significant efficacy with single component vaccines, extremely potent antibody or T cell responses are generally required.

Faced with these challenges for subunit vaccine development some new whole parasite vaccine approaches are being explored but these face substantial challenges in manufacture, deployment and delivery.

The most advanced malaria vaccine is the RTS,S vaccine developed by GSK Biologicals from 1988 to phase III trial in African children (3-6) and pilot implementation studies will be starting in 2018. This vaccine induces very high antibody responses that bind to the major surface component of the malaria sporozoite, the circumsporozoite protein, and thereby prevent or reduce parasite entry into the liver (7). Much of the RTS,S immune response is induced to hepatitis B surface antigen rather than to the malaria components of the particle. Nonetheless, this is the most effective single component vaccine tested for malaria and when combined with the saponin +MPL liposomal adjuvant AS01 reliably induces about 45-60% sterile efficacy in sporozoite challenge studies (8), with significant but modest levels of efficacy in field trials (3).

While the initial goal of developing a first generation malaria vaccine with up to 50% short-term efficacy appears close, a highly effective malaria vaccine is still a major objective of global health research, and will likely require a multi-stage product. In recent years there has been substantial progress in the development of single antigen pre-erythrocytic vaccines that point to the feasibility of developing a high efficacy vaccine that could make a major impact on malaria control.

MultiMalVax built on recent advances in the malaria vaccine field which addressed each of the three life stages of the Plasmodium falciparum parasite, namely:

• The availability of a new vectored vaccination regime based on the chimpanzee adenovirus (ChAd63) - modified vaccinia Ankara (MVA) prime-boost approach to induce exceptionally potent CD8+ T cell responses and high titre antibodies against multiple malaria antigens;
• The development of a potentially improved version of the leading partially protective RTS,S sporozoite vaccine candidate, termed R21, that lacks the excess of Hepatitis B virus surface antigen (HBsAg) seen in RTS,S;
• The identification, using a viral vector technology screen, of the blood-stage antigen PfRH5 as the first antigen to induce potent strain-transcending neutralisation of blood-stage parasites in in vitro growth inhibition assays;
• The demonstration that vector-induced antibodies against two mosquito-stage antigens can induce very potent transmission blocking against field isolates of P. falciparum in Africa

The overarching aim of the MultiMalVax clinical development programme was to develop the concept of a highly effective multi-stage malaria vaccine to the point of proof-of-concept phase II efficacy testing in Europe, prior to field trials in malaria-endemic areas. MultiMalVax undertook phase I / II clinical trials to assess the pre-erythrocytic, blood-stage and mosquito-stage components individually or together, using state-of-the art immunomonitoring, key functional assays of vaccine-induced immunogenicity, and sporozoite and blood-stage parasite challenges to demonstrate vaccine safety, immunogenicity and efficacy.

Individual objectives were to:

1. Manufacture viral vector vaccines based on a chimpanzee adenovirus ChAd63 and MVA expressing the
o reticulocyte-binding protein homologue 5 (PfRH5) blood-stage antigen
o Pfs25 mosquito-stage antigen.
2. Manufacture a potentially improved version of the clinically validated pre-erythrocytic-stage protein particle vaccine RTS,S (called R21), displaying a higher number of antibody target epitopes per particle. R21 and RTS,S are both based on the P. falciparum circumsporozoite protein (CSP) fused to HBsAg, a protein capable of forming virus-like particles.
3. Conduct phase I/II clinical trials addressing safety, immunogenicity and efficacy of:
o A virus-like particle pre-erythrocytic-stage vaccine, alone and in combination with viral vector vaccines expressing the thrombospondin related adhesive protein (TRAP), another pre-erythrocytic-stage vaccine;
o PfRH5 blood-stage vaccine;
o Pfs25 mosquito-stage vaccine;

o A combination of vaccines targeting two or more life-stages, depending on the success of earlier trials targeting individual life-stages.

MultiMalVax undertook a series of phase I / II clinical trials to assess the pre-erythrocytic, blood-stage and mosquito-stage components individually, and then together, combining the efficacious vaccines from different stages. This collaboration of academic and industrial partners together with the major European product development partnership for malaria vaccines provided complementary and highly relevant abilities to accelerate development of this promising product.
For each clinical trial, detailed analysis of immunogenicity and mechanism of action was carried out.

Project Results:
4.1.3 Main S&T results/foregrounds
The aim of MultiMalVax was to develop the concept of a highly-effective multi-stage malaria vaccine to proof-of-concept phase IIa efficacy testing in Europe, prior to clinical trials in malaria-endemic regions. The MultiMalVax activities were divided into ten work packages that supported the clinical development of the malaria vaccine candidates targeting all malaria life-cycle stages in the human host. In addition, the proof-of-concept for the in vitro-killing assays was established. The following describes the results of the MultiMalVax project.

4.1.3.1 Vector generation, vaccine manufacture and thermostability studies
Viral vector generation and manufacture
During the first year a set of different vectors were constructed and tested for the immunogenicity to select the candidate for manufacturing and clinical testing.
- ChAd63 and MVA vectors encoding the Plasmodium falciparum reticulocyte-binding protein homologue 5 (RH5)
- ChAd63 and MVA vectors encoding the mosquito-stage antigens were generated:
o expressing both Plasmodium falciparum Pfs25 and Pfs230C either as a fusion protein separated by a flexible linker or as a single gene
o expressing Pfs25 fused to IMX313.

In order to down-select the vaccine candidates, mice were immunised with the various vectored vaccines and strong T cell and antibody responses were confirmed. Transmission blocking activity induced by the different mosquito-stage antigens was also confirmed in a standard membrane feeding assay (SMFA) with ChAd63_MVA Pfs25-IMX313 showing the best activity.

The GMP batch of ChAd63-RH5 was produced Advent / Okairos in Rome. ChAd63-Pfs25-IMX313 was manufactured at the Clinical BioManufacturing Facility in Oxford. MVA-RH5 and MVA- Pfs25-IMX313 were GMP manufactured at IDT Biologika (IDT) in Germany as described in section 4.1.3.3 and 4.1.3.4.

R21 particle manufacture and thermostability studies
Within MultiMalVax, the production parameters for the pre-erythrocytic vaccine candidate R21 have been defined, followed by a GMP manufacture of R21 to be used in phase I and II clinical trials. Upstream manufacture of R21 was undertaken in Pichia pastoris and downstream purification was achieved using affinity purification (see 4.1.3.2). Immunogenicity of adjuvanted R21 was demonstrated in mice, and sterile

protection of varying levels up to 100% was shown in a transgenic parasite model depending on the adjuvant used. Current efforts are on-going to further develop a sugar-membrane technology as a potential approach for distribution of R21 vaccine at ambient temperature in malaria-endemic regions, without the requirement for cold-chain storage. Initial experiments performed within MultiMalVax are promising.

4.1.3.2 Pre-erythrocytic stage malaria vaccine candidate R21

Safety and immunogenicity of a protein particle malaria vaccine candidate, R21, administered with AS01B in healthy UK volunteers (VAC056):

R21 has been developed at the Jenner Institute, University of Oxford (WP2). R21 is produced by using recombinant Hepatitis B S Antigen (HBsAg) particles expressing the central repeat and the C-terminus of the circumsporozoite protein (CSP) and has been GMP manufactured in Pichia pastoris. This is a similar protein particle to GSK's RTS,S which also targets the pre-erythrocytic circumsporozoite protein, the major functional protein in sporozoite development and hepatocyte invasion. R21 has been demonstrated in pre-clinical studies to be safe, non-toxic and immunogenic. R21 lacks the excess of HBsAg in RTS,S and has been shown to be highly immunogenic and to have at least comparable immunogenicity and a similar high level efficacy as RTS,S in animal studies.

Figure 1: Graphical illustration of R21 and RTS,S

Manufacture of clinical grade R21 particle was undertaken at the University of Oxford's CBF as part of work package 4 (WP4). R21 is similar to the RTS,S vaccine where the R21 particle contains only P. falciparum antigen sequences that are present in RTS,S. It is a hybrid protein consisting of the majority of the CS protein of P. falciparum fused to the hepatitis B surface antigen. It spontaneously forms a particle in a similar way as RTS,S. In pre-clinical studies, it induces predominantly malaria rather than hepatitis antibodies probably because it has a higher proportion of malaria to hepatitis antigen than RTS,S. This is made possible by expressing R21 in the better expressing yeast Pichia pastoris, rather than in Saccharomyces cerevisiae. At the C-terminus of R21, a four amino acid sequence has been added, EPEA, which is required for efficient immunochromatographic purification of R21. This very short sequence is coincidentally found many times in the proteome of malaria parasites and humans but has not, to our knowledge, been used previously as a vaccine component. The Medicine and Healthcare products Regulatory Agency (MHRA) approved the phase I clinical trial in October 2015 and the clinical trial commenced in December 2015. R21 adjuvanted with AS01B was administered to 20 healthy volunteers in Oxford and Southampton in this phase I trial VAC056 (NCT02600975). All vaccinations were administered intramuscularly in a three-dose regime with vaccinations given 4 weeks apart. Participants were followed up for 6 months after their final vaccination. VAC056 is now completed and the last participant visit took place in January 2017. There were no safety concerns relating to R21 in GSK's AS01B adjuvant and both doses were well tolerated. R21 in AS01B was immunogenic and induced good antibody responses to the pre-erythrocytic circumsporozoite protein at both 10 and 50µg doses tested, which was comparable to levels induced by the leading malaria vaccine candidate, RTS,S. The trial manuscript is currently in preparation for publication.

VAC056 trial design:

Week 0 4 8

Group 1 (n=10) 10µg R21/AS01B 10µg R21/AS01B 10µg R21/AS01B

Group 2 (n=10) 50µg R21/AS01B 50µg R21/AS01B 50µg R21/AS01B

Initial immunogenicity profiles observed are very encouraging and it induces strong antibody responses to the CSP central repeat, at levels comparable to those induced by the leading malaria vaccine candidate, RTS,S. The results of this clinical trial will be published in a scientific journal in 2017.

4.1.3.3 Blood-stage malaria vaccine candidate RH5

A Phase Ia clinical trial to assess the safety and immunogenicity of new Plasmodium falciparum malaria vaccine candidates ChAd63 RH5 alone and with MVA RH5 (VAC057)

This Phase Ia trial (NCT02181088) is a dose escalation, first-in-human trial of the viral vectored P. falciparum blood-stage malaria vaccine candidates ChAd63 RH5 and MVA RH5 in a heterologous prime-boost regimen. The reticulocyte homologue (RH5) is the first known target within the P. falciparum blood-stage merozoite to be susceptible to vaccine-induced broadly neutralising polyclonal antibody (9). It is released from the rhoptry organelles and shown to form an essential interaction with basigin (CD147) on the erythrocyte surface (10).

Figure 2: Graphical illustration of RH5 interactions

This completed clinical trial was conducted in Oxford and Southampton in healthy volunteers aged 18 – 50 years. The total number of volunteers planned for enrolment in the study was 24, with 16 of them receiving both vaccines. ChAd63 RH5 was given as a prime vaccination with the MVA RH5 boost given 8 weeks later. The first 8 volunteers received ChAd63 RH5 alone as part of the dose escalation study design. ChAd63 is a replication-deficient simian adenovirus and MVA is modified vaccinia virus Ankara, which is also unable to replicate in humans. Both encode the P. falciparum reticulocyte-binding protein homologue 5 (RH5), which is one of the proteins involved in parasite invasion of red blood cells. This protein is vital for survival of the parasite and the binding of this protein to its receptor (basigin) mediates an essential interaction required for red blood cell invasion by all tested strains of P. falciparum to date. ChAd63 and MVA vectors encoding RH5 were previously generated and evaluated in work package 1 (WP1). The ChAd63/MVA RH5 vaccines were manufactured to current Good Manufacturing Practice (cGMP) in WP 3 and subsequently used in this Phase Ia clinical trial VAC057 (WP7). ChAd63 RH5 was manufactured by Advent in Italy and MVA RH5 by IDT Biologika GmbH, Germany. Final batch certification and associated labelling of both vaccines took place at the CBF, University of Oxford. Pre-clinical testing of the vaccine demonstrated high efficacy against a heterologous strain challenge. In this trial the safety and cellular and humoral immunogenicity of this vaccination regimen were assessed. ChAd63/MVA RH5 vaccines were shown to be safe and immunogenic in healthy volunteers. Purified IgG from trial volunteers inhibited P. falciparum growth, as assessed by a growth inhibition assay (GIA). This is the first antigen to induce substantial cross-strain GIA following viral vectored vaccination in a clinical trial. The manuscript detailing the results of this clinical trial is currently in preparation. An effective RH5 vaccine is likely to require higher levels of antibodies than were induced by ChAd63/MVA RH5. A protein-in-adjuvant formulation (RH5.1) is currently being evaluated in a phase I/IIa clinical trial in the UK.

4.1.3.4 Transmission blocking/Mosquito stage malaria vaccine candidate Pfs25

A Phase Ia clinical trial to assess the safety, immunogenicity and ex-vivo efficacy of new Plasmodium falciparum malaria vaccine candidates ChAd63 Pfs-IMX313 alone and with MVA Pfs25-IMX313 (VAC062):

A call for a suitable European clinical trial site was advertised in Q 2/3 2014, to conduct a phase I clinical

trial to assess the safety, immunogenicity and ex-vivo efficacy of simian adenovirus (ChAd63) and Modified Vaccinia Ankara (MVA) vectors expressing a mosquito-stage Plasmodium falciparum antigen. The trial was to initiate in the first half of 2015. Of the four applications received, Southampton NIHR Wellcome Trust Clinical Research Facility was selected as the trial site.
The phase I clinical trial VAC062 is the first clinical use of the viral vectored transmission blocking/mosquito stage vaccines ChAd63 Pfs25-IMX313 and MVA Pfs25-IMX313. The transmission-blocking Pfs25 antigen is fused to the Imaxio IMX313 carrier protein. Fusion to the IMX313 DNA sequence leads to oligomerisation of the recombinant protein as the IMX313 carrier protein spontaneously auto-assembles into a heptamer. The oligomerisation of the antigen is expected to induce significantly enhanced B cell and T cell immunogenicity.

Figure 3: Graphical illustration of the prime boost approach and the IMX313 oligomerised heptamer
This phase I trial in healthy volunteers aged 18 – 50 began in 2015 and is currently ongoing in Southampton and Oxford, UK (NCT02532049). Previous trials using the Pfs25 antigen have been conducted in other centres as protein-in-adjuvant vaccines but not with viral vectors. The total number of volunteers planned for enrolment in the study was 24, with 16 of these receiving both vaccines. ChAd63 Pfs25-IMX313 was given as a prime vaccination with the MVA Pfs25-IMX313 boost given 8 weeks later. The first 8 volunteers received ChAd63 Pfs25-IMX313 alone as part of the dose escalation study design. ChAd63 and MVA vectors encoding Pfs25-IMX313 were previously generated and evaluated as part of WP1. The ChAd63/MVA Pfs25-IMX313 vaccines were manufactured to cGMP as part of WP3 and subsequently used in the VAC062 clinical trial (WP8). ChAd63 Pfs25-IMX313 was manufactured under cGMP conditions at The Clinical Biomanufacturing Facility (CBF) (www.cbf.ox.ac.uk) University of Oxford and the MVA Pfs25-IMX313 was manufactured by IDT Biologika GmbH, Germany. To date, all clinical trial participants have been enrolled, all vaccinations are complete and the final volunteer follow-up is planned for June 2017. There have been no safety concerns relating to the vaccines and they have been well tolerated. Immunogenicity analysis is ongoing and we have demonstrated that antigen-specific T cells as well as antibodies are induced after vaccination. Further work is being performed to define the levels of antigen-specific antibodies induced and the ex-vivo function of these antibodies by a standard membrane feeding assay (SMFA).
4.1.3.5 Combination malaria vaccine candidate
A Phase I/IIa Sporozoite Challenge Study to Assess the Safety and Protective Efficacy of adjuvanted R21 at two different doses and the Combination Malaria Vaccine Candidate Regimen of adjuvanted R21 + ChAd63 and MVA encoding ME-TRAP (VAC065):
Combination vaccine efficacy trial (WP9): Vaccine efficacy was previously demonstrated in the phase IIa malaria challenge trials (VAC055 and VAC059) using the viral vectors ChAd63/MVA expressing the liver stage antigen ME-TRAP in combination with GSK's pre-erythrocytic stage vaccine RTS'S. The same viral vectors encoding ME-TRAP were then selected in combination with R21 in adjuvant (Matrix M) for the final combination efficacy trial VAC065 (NCT02905019) taking into consideration the immunogenicity data generated from the R21 trials (VAC053 and VAC056). The trial design for VAC065 was discussed and agreed by the consortium partners and the Independent Scientific Advisory Committee (ISAC) members.
The VAC065 trial design:

The safety, immunogenicity and efficacy of R21 adjuvanted with Matrix-M1 in comparison to R21/Matrix-M1 in combination with ME-TRAP vectored vaccines is currently being assessed in this phase I/IIa

challenge trial. The R21 vaccine targets the sporozoite stage of infection and this is used in combination with the heterologous prime boost viral vector vaccine regimen of ChAd63-MVA ME-TRAP, which targets the liver-stage of infection. The total number of volunteers planned for enrolment in this malaria challenge trial was 36 plus 6 unvaccinated controls. VAC065 is currently ongoing in healthy volunteers aged 18-45 where a total of 31 volunteers in Oxford and Southampton plus 6 controls underwent a malaria mosquito bite challenge (CHMI) on the 30/31st January 2017. The results of this clinical trial will be published in a scientific journal this year.

4.1.3.6 In vitro killing assays

The importance of CD8+ T cells in protection against pre-erythrocytic stages of malaria infection (11, 12) has been demonstrated repeatedly in rodent models, using knock-out mice, in vivo depletion or adoptive transfer of CD8+ T cells (13), particularly with radiation-attenuated sporozoites. The residence of CD8+ memory T cells in the liver has been shown to correlate with protection in mice and a threshold of memory CD8+ T cells has been defined above which protection could be predicted in individual mice (14). In humans, evidence of a protective role for CD8+ T cells is more descriptive because of practical and ethical limitations, however the finding of a strong correlation between vaccine-induced IFNγ-secreting CD8+ T cell responses targeting the liver-stage antigen TRAP and efficacy against malaria (15) provides a new system in which to study the interaction between hepatocytes, sporozoites and T cells. Mechanisms contributing to parasite killing in the human liver are still poorly characterised because of the difficulty of establishing efficient in vitro systems that support the exo-erythrocytic development of P. falciparum. However, UPMC have unrivalled experience in growing P. falciparum liver-stage parasites in human hepatocytes and have used these to study mechanisms of hepatocyte invasion and assess the antimalarial activity of novel compounds (16-18).

In addition, based on a murine model of vaccine-induced CD8+-mediated immunity using genetically attenuated parasites, Trimnell et al. established that killing of infected hepatocytes was elicited through a contact-dependant mechanism involving both IFNγ and perforin, which resulted in death of both hepatocyte and parasite (19). Although the relationship between antigen-specific IFNγ-secreting CD8+ T cells and protection was demonstrated, proof-of-concept of the ability of these cells to kill parasites directly would be central to understanding how protection is mediated in vivo.

Within MultiMalVax, a combination of the techniques was applied to studying vaccine-induced protective efficacy against malaria. This work provided the unique opportunity to demonstrate that human CD8+ T cell induced by subunit vaccination can directly kill parasites in liver cells, a long standing goal in malaria vaccine research. It will also allow us to investigate at the cellular level how protective immunity varies between completely and partially protected vaccinated volunteers.

This WP was a strong collaboration of the teams at UPMC and UOXF. The in vitro parasite killing assay with primary human hepatocytes (HH) was set up with the aim to validate a correlate of protection for the pre-erythrocytic stage malaria vaccine. While first assays were done with fresh and cryopreserved human hepatocytes obtained at UPMC, assays are now performed with commercially available cryopreserved human hepatocytes. An optimised protocol for HH culture was established. The development of parasite liver-stages in these cells was validated and a system set up for automated parasite counting. Additionally, the protocol for the purification of parasite-specific CD8 T cells from the PBMC of vaccinated volunteers and the stimulation were optimised. A peptide negative control was included in the assays.

The functional assays were used to assess the cytotoxicity of CD8 T cells from immunised human volunteers towards the liver stage of P. falciparum in HLA-A-matched hepatocytes. Assays with this optimised protocol were performed with PBMCs from volunteers showing convincing evidence of antigen specific functional activity of CD8+ T cells form ME-TRAP immunised vaccinees in these experimental conditions. Additional work is planned to further optimise the assays further and to allow the analysis of additional samples. This work is being prepared for publication and will be continued in the new EU H2020 funded project OptiMalVax.

4.1.3.7 Management and Coordination
The consortium management tasks in WP10 were to ensure that the project was conducted efficiently within the predetermined timing and budget, to establish management tools and methods for communication with the EC and between participants and for monitoring progress towards objectives, deliverables and milestones, to prepare regular EC progress, financial and management reports as well as a final report of the results, to organise meetings as necessary and to conduct the financial and administrative management of the project.

In 2012, the MultiMalVax project management and monitoring committee was established with Prof Adrian Hill as Coordinator who was assisted by the project managers from UOXF and EVI. A Consortium Agreement was prepared and negotiated with the project beneficiaries and was fully executed in June 2012. The Project Steering Committee (PSC) and Independent Scientific Advisory Committee (ISAC) were appointed.

The project kick-off meeting was held on 08 November 2012 in Oxford, UK; the first MultiMalVax annual meeting was held in November 2013 in Heidelberg, Germany. The second annual meeting was held in September in Siena, Italy, followed by meetings in November 2015 in Ottignies-Louvain-la-Neuve, Belgium and in March 2017 in Oxford, UK. The latter meetings were attended by the ISAC who provided advice to the coordinator and PSC on project activities.

Ad hoc ISAC telephone conferences were scheduled when needed. Regular PSC teleconference meetings have been held in order to ensure progress and communication between participants.

Annual, Periodic, Final and Financial reports were submitted to the EC according to timelines in the grant agreement.

Potential Impact:
4.1.4 Impact, dissemination activities and exploitation results

Impact:
A highly effective malaria vaccine is recognised as a major tool urgently needed to improve malaria control, as current tools become less effective with increasing antimalarial drug resistance and increased resistance of mosquitoes to spraying and to the insecticides of bed nets.

Development of a malaria vaccine has been one of the major goals of global health research for several decades. With the entry of RTS,S/ AS01 into large scale phase III testing and the recommendation by the

World Health Organization's Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) for roll out of RTS,S/ AS01 in limited pilot demonstrations in Africa, the initial goal of developing a first generation malaria vaccine with up to 50% short-term efficacy appears closer. However, the planned implementation trials of RTS,S/AS01, due to start in 2018, are scheduled to last 3-5 years so licensure of that vaccine candidate cannot happen before the 2020s. In addition there are some significant logistic and safety issued to be addressed.

Scientific literature agrees that a final malaria vaccine will likely be a multi-stage vaccine that adopts a multi-hit approach. This has several advantages: a) It overcomes the difficulty of achieving very high level efficacy with single-stage vaccines, which has proven very difficult in practice; and b) it allows the potential synergies between vaccine components acting at different stages of the life-cycle to be exploited. Pre-clinical models provide strong evidence that combining anti-sporozoite and anti-liver stage components can provide synergistic efficacy. Another advantage of a multi-stage approach is the reduced possibility of escape mutations being selected. A parasite with a variant that allows escape from one immune response will still be susceptible to immunity against other components. And, finally, the various components should synergise to facilitate interruption of malaria transmission, an increasingly recognised important goal of malaria vaccination. For mosquito-stage antigens it might be difficult to provide very high transmission blocking efficacy if used alone, but combined with protective sporozoite and liver-stage components the overall transmission blocking effect should be very substantial.

A great attraction of the MultiMalVax multi-stage approach was that it combined some of the most promising antigens and delivery systems for each stage of the life-cycle. For the sporozoite stage RTS,S has been shown to be currently the most effective candidate and R21 is a biosimilar produced in the improved Pichia expression platform. The clinical trials to date of R21 in two different adjuvants have been very encouraging and this could well be developed as a stand-alone anti-sporozoite vaccine candidate. Discussions with a potential commercial licensee are underway. The ChAd-MVA vectored approach with the ME-TRAP insert has proven to be highly effective at inducing high level CD8+ T cells in humans and has provided the promising liver-stage efficacy to date, especially in African trials. RH5 is a new very promising conserved blood-stage antigen and this project has provided the first evidence that this antigen is safe as a vaccine antigen in humans and can induce cross-strain growth inhibitory activity. However, protein-in-adjuvant formulations may be required for substantial efficacy. Finally, the first trial of vectored transmission blocking vaccine has demonstrated immunogenicity for both antibodies and T cells. Results of this project have shown a favourable safety profile of all these vaccine candidates and detailed immunogenicity results are expected soon.

Exploitation:
The estimated cost of goods of the proposed multi-stage vaccine when manufactured at scale, and the cost for all components for a full immunisation course should be affordable, and meet the GAVI cost limit. We therefore anticipate that this vaccine could be cost-effectively manufactured to meet the global annual need for about 100 million courses of vaccine in developing countries. Additionally, a highly effective vaccine should have a significant market for military forces and travellers which increases the commercial interest of this product.

The consortium was exceptionally well placed to develop the combination vaccine and we have been

successful in this programme of work which ended in in March 2017. The next step was then to evaluate a combination vaccine at sites in malaria endemic regions in Africa. Further work is ongoing to develop these and improved combination vaccines further and test these in a new EC funded programme, OptiMalVax.

Dissemination:
The MultiMalVax consortium established a clear communication plan that was followed through the life cycle of the project. Materials for public dissemination were generated and distributed on different occasions. Scientific achievements were communicated to scientific and general public communities during international conferences and events. Project background, objectives and achievements on the website are readily accessible to both specialists and the general public. The website has been continuously updated with information on relevant project events and scientific progress. Additionally, a summary of the MultiMalVax project is available on the EVI website: http://www.euvaccine.eu/portfolio/project-index/multimalvax. EVI issued a leaflet giving an overview of the project background, objectives, milestones and up to date achievements to be distributed to the general public during international scientific or public events. Project progress and major achievements were published annually in the EVI annual report for donors and stakeholders thus giving visibility of MultiMalVax to other potential donors and funding agencies.

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4.1.5 References
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Documents connexes

final1-multimalvax-final-report-final-170526.pdf

Dernière mise à jour: 24 Juillet 2017

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