ANNUAL REPORT 2011

For Donors

Version 1.0 - 17 March 2012

Table of Contents

List of Abbreviations

ACT	Artemisinin Combination Drug Therapies
Ad	Adenovirus
AdCh	Simian adenovirus
AIDS	Acquired Immune Deficiency Syndrome
AMA	Apical Membrane Antigen
BC	Brighton Collaboration
BoS	Board of Stakeholders
BPRC	Biomedical Primate Research Centre
cGMP	current Good Manufacturing Practice
CoI	Conflict of Interest
CSP	Circumsporozoite Protein
DALY	Disability Adjusted Life Year
DANIDA	Danish Development Agency
DCGI	Drug Controller General of India
DGIS	Directorate General for International Cooperation (at Ministry of Foreign Affairs, The Netherlands)
DiCo	Diversity Covering
DKK	Danish Kroner
DNA	Deoxyribonucleic Acid
EC	European Commission
EDCTP	European and Developing Countries' Clinical Trials Partnership
EEA	European Economic Area
EEIG	European Economic Interest Grouping
EMVDA	European Malaria Vaccine Development Association
EMVI	European Malaria Vaccine Initiative (now European Vaccine Initiative)
EU	European Union
EVI	European Vaccine Initiative

FP6 & FP7	Framework Programme 6 & 7
GAAP	Generally Accepted Accounting Principles
HIV	Human Immunodeficiency Virus
ICGEB	International Centre for Genetic Engineering and Biotechnology
IDEA	African-European Research Initiative on Co-infections of Poverty Related and Neglected Infectious Diseases
IEC	Independent Ethics Committee
INCO DC	International Cooperation Research Programme with Developing Countries
INYVAX	Optimisation of the Development of Poverty Related Diseases Vaccines by a Transversal Approach, Addressing Common Gaps and Challenges
ISHReCA	Initiative to Strengthen Health Research Capacitiy in Africa
KEMRI	Kenyan Medical Research Institute
LMIC	Low and Middle Income Countrie
LoI	Letter of Interest
MDG	Millennium Development Goals
MoU	Memorandum of Understanding
MRC	Medical Research Council
MSP	Merozoite Surface Protein
MVA	Modified Vaccinia Ankara
MVAF	Modern Vaccines/Adjuvants Formulation
MVI	Malaria Vaccine Initiative
MVVC	Malaria Vectored Vaccines Consortium
MVW	Malaria Vaccines for the World
NTD	Neglected Tropical Disease
OECD	Organisation for Economic Co-operation and Development
OPTIMALVAC	Initiative on Optimising Malaria Vaccine Lab Assays Evaluation
PHARVAT	Platform for the Harmonization of Vaccine Adjuvant Testing
PNL	Profit and Loss
PRD	Poverty Related Diseases
R&D	Research and Development
RI	Research Infracstructure
RNA	Ribonucleic Acid
SAC	Scientific Advisory Committee
Sida/SAREC	Swedish Development Agency/ Swedish Committee for Research on developing countries
SSI	Statens Serum Institut

TB	Tuberculosis
TBVI	TuBerculosis Vaccine Initiative
TRANSVAC	European Network of Vaccine Development and Research
USA	United States of America
WHO	World Health Organization
WP	Work Package

Foreword by Professor Bartram, Dean of the Medical Faculty of Heidelberg

In 2009 Heidelberg University became one of the two founding fathers of European Vaccine Initiative – European Economic Interest Grouping (EVI-EEIG) together with Stockholm University, in recognition of the international importance of EVI in the field of vaccines to fight Diseases of Poverty. It was therefore not without pride that Heidelberg University was also chosen as the hosting institution. In 2010 EVI-EEIG welcomed four additional prestigious European institutions: Biomedical Primate Research Centre (BPRC), The Jenner Vaccine Foundation, Royal College of Surgeons in Ireland (RCSI) and the National Institute for Public Health and the Environment (RIVM).

Research in infectious diseases constitutes one of Heidelberg University's core areas, and with the planning of a centre for integrative research in infectious diseases, the university intends to strengthen this focal point further. Heidelberg University is particularly strong in basic science and now, with the support of EVI, hopes to reinforce the translational effects (from promising technologies into clinical practice). To this end, EVI's expertise in the development of new vaccines will be of great importance for Heidelberg University's participation (e.g. research groups involved in malaria and HIV) in the newly founded German Centre for Research in Infectious Diseases (DZIF).

It is also important to note that during the year EVI, through the TRANSVAC consortium, has been active in leading the development of a vaccine research infrastructure roadmap in Europe.

EXECUTIVE SUMMARY

2012 was the year of resurgence of EVI, with renewed funding from Irish Aid and the award from the German Government "Bundesministerium für Bildung und Forschung (BMBF)" for development of vaccine candidates against Pregnancy Associated Malaria.

The most exciting event last year was undoubtedly the first EVI Rendez-Vous held in November. It bought together more than 50 external participants from a wide range of universities and international institutions covering among other fields, research, public health, industry and finance. As a result of its success, another Rendez-Vous will be held this year 6 December 2012 over a full day.

All the vaccine candidates (P27A, CSVAC, AMA1-DiCo and JAIVAC-1) undergoing product and clinical development, which constitutes EVI's core activity, are on track, and no major problems were encountered in 2011. The phase I clinical trial of **JAIVAC-1** was concluded in November with no Serious Adverse Events observed. The clinical development work on **AMA1-DiCo** was advanced this year, and a phase I clinical trial will commence in 2012. **CSVAC** has already entered into a phase I clinical trial, and **P27A** is moving towards production of a clinical lot.
The **MSP3** vaccine of Institut Pasteur has shown promising efficacy results in a clinical trial in Burkina Faso. This long synthetic peptide was originally funded by EVI.

The projects funded by the European Commission (EC) and the European and Developing Countries Clinical Trials Partnership (EDCTP) are developing according to the plans, and the most notable achievements in 2011 are as follows:
EMVDA: The successful Good Manufacturing Practice (GMP) clinical batch production of vaccine candidates MSP1 and pfPEBS (formerly SR11.1).
IDEA: Vaccine activities commenced in Q1 2011. The assessment of the impact of helminth infections on the immune response to the GMZ2 malaria vaccine candidate is performed in clinical trials at the Albert Schweitzer Hospital, Lambaréné, Gabon. The annual meeting with all project partners was held in September.
INYVAX: The guidelines for assessing the safety of malaria and tuberculosis vaccines in pre-licensure clinical trials have been developed. The INYVAX decision tree for the

formulation of vaccines with adjuvants have been publicised in several international conferences. Thirty students sponsored by INYVAX have attended the ADVAC course.

MVVC: according to the plans, the phase Ib clinical trials in adults were conducted at the Medical Research Council (MRC) Gambia and Kenya Medical Research Institute (KEMRI) Kilifi respectively, and were followed by the phase Ia clinical trial in children aged 2-6 years at MRC Gambia.

OPTIMALVAC: The position paper "Towards validated assays for key immunological outcomes" was published and is freely available.

PHARVAT: The project was successfully concluded with an adjuvant reference kit being made available to stakeholders. A paper is being drafted for publication in a peer reviewed journal.

TRANSVAC: The successful Mid Term Review in October, the main conclusions being that the project is on schedule and that 11 applicants for Transnational Access was deemed very satisfactory. The first successful TRANSVAC stakeholder workshop was held in Brussels. The two main topics were I) How to make Translational Research in Vaccine more attractive, II) How to increase training in vaccinology.

In the past EC/EDCTP projects have been dealt with individually, but this year a new approach has been introduced, whereby all EVI's work is detailed in categories: a) Introduction, Vaccine Description, Background, Team, b) Preclinical Process, Production, Investigational Medicinal Product Dossier (IMPD), c) Delivery Platform, Adjuvants, Viral Vectors, d) Clinical Development, e) Capacity Building, Workshops, Training, f) Harmonisation g) Outreach Communication. It is hoped that this new approach will give the reader a much better comprehension of the depth and breadth of EVI's activities, and how the various projects interact.

Pleasant reading.

Odile Leroy, Executive Director

THE YEAR IN GENERAL

2011 was the year when we finally said goodbye to European Malaria Vaccine Initiative (EMVI). In July EMVI was officially dissolved by written procedure in an announcement by the former Chair of the EMVI Board, Hannah Akuffo to former Board members and other relevant stakeholders http://www.euvaccine.eu/news-events/news/european-malaria-vaccine-initiative-emvi-formerly-dissolved.

Transfer of EMVI activities and assets to EVI

The process of the transfer of EMVI activities and asset has been finalised between Statens Serum Institut (SSI) and EVI, whereby responsibility for all EMVI activities including GMZ2 project has reverted to EVI.

General

Two new Memoranda of Understanding have been signed: the first one with the Brighton Collaboration Foundation and the second one with the Malaria Vaccine Development Program. http://www.euvaccine.eu/partnerships/memoranda-understanding-and-intent

EVI has issued its first call in November, which was directed towards European and Developing Countries' research groups, who were invited to submit full proposals for the continued development and clinical testing of vaccine candidates against diseases of poverty. The deadline for submission was 10 February 2012.

On the 4th World Malaria Day, 25 April, EVI published its first News Letter. The second was published in July and the third will be published early in 2012. News letters can be found on the EVI web site http://www.euvaccine.eu/about-us-0.

Fundraising

EVI was extremely pleased with a new five year funding grant by Irish Aid. Irish Aid is the Government of Ireland's programme of assistance to developing countries. This grant will allow EVI to continue calling for Diseases of Poverty vaccine candidates in the foreseeable years. Furthermore, as the only vaccine developer, EVI has been successful in its response

to a German call -Bundesministerium für Bildung und Forschung (BMBF) - for project specific co-funding for Pregnancy Associated Malaria vaccine candidate.

In response to European Commission call (EC) FP7-HEALTH-2012-INNOVATION-1, EVI is more than happy to have three proposals that have passed the first round.
EVI also responded to the third call of the Norwegian INDIGO Partnership Programme, for research projects in the field of biotechnology applied to Human Health. EVI will know whether they have passed the first round by mid-February.

Staff

During the year the Heidelberg office was strengthen with new staff members. Thorsten Kohaut, who deals with EVI's day to day financial transactions, and Mark Geels and Nicola Viebig who are Project Managers. Joel Thøgersen became a full member of the team as Trainee Project Manager in August after working part time as a student. Odile's new Personal Assistant, Sandra Theilig began duties in September, Regitze Louise Thøgersen was promoted to Programme Manager, and Nathalie Imbault Quality Assurance and External Relations and Communication Director. Jill Iversen, who has been with EVI from its inception, retired at the end of October, but remains available for the web site and ad hoc tasks. The total number of staff, including consultants, as at 31 December is 14.
In September the annual team building event took place in France, assisted by external consultants. The main team goals were to improve integration activities within EVI projects, and exchange of expertise/experience, be a part of the big picture, and to find ways to make EVI expertise available to all relevant parties.

EVI Rendez-Vous

On 14 November EVI held a highly successful scientific Rendez-Vous in which all EVI's governing bodies (EVI EEIG-Board, Board of Stakeholders, Scientific Advisory Committee and staff) participated, plus more than 50 external participants from industry and a wide range of universities and international institutions covering among other fields, research, public health, finance link.

EVI EEIG-Board, Board of Stakeholders (BoS) and Scientific Advisory Committee (SAC)

The Rendez-Vous was followed by EEIG-Board, BoS and SAC meetings. These three governing bodies also held face-to-face meetings in March. At the Board meeting Sir Brian Greenwood announced that this would be his last meeting as he was leaving the Jenner Vaccine Foundation (JVF). He has been replaced by the new Chair of JVF, David Salisbury. EVI extends grateful thanks to Sir Brian Greenwood for his active support for EVI.

INTRODUCTION

EVI Projects

AMA1-DiCo

Partners
European Vaccine Initiative, DE
Biomedical Primate Research Centre, NL
Confarma, FR
European Vaccine Initiative, DE
Fraunhofer IME, DE
Gregory Fryer Associates Ltd, UK
Henogen Novasep, BE
Infectious Diseases Research Institute, USA
NNE Pharmaplan GmbH, DE
Nova Laboratories, Ltd, UK
Output Pharma, DE

Apical Membrane Antigen 1 (AMA1) is a leading candidate for a vaccine against *Plasmodim falciparum*. Recombinant proteins representing the whole ectodomain (Domains I – III) of *Plasmodium falciparum* AMA1 can induce antibodies that recognise native parasites and inhibit merozoite invasion of erythrocytes in vitro.

To investigate the role of human antibodies in naturally acquired immunity, children in three separate endemic populations were analysed for reactivities prior to a malaria transmission season and whether or not they suffered an episode of malaria throughout the subsequent transmission season. Recombinant proteins representing the different domains of AMA1 were used to dissect the antibody reactivities in detail. In two different communities in Kenya, antibodies against domain I were significantly associated with protection from subsequent malaria infections, in both univariate analyses and after adjusting for age. One of the Kenyan cohorts and a separate Gambian cohort antibodies to domain II were also associated with protection. However, for the Kenyan cohorts the protective associations of antibodies were only seen among the subjects that were parasite slide positive at the time of pre-season serum sampling, a phenomenon noted in previous studies from this area on

antibodies to the infected erythrocyte surface. Antibodies to domain III were very rare in all populations. Results support the development of AMA1 as a vaccine candidate and particularly the inclusion of domains I and II to induce antibody responses. They also highlight the importance of conducting prospective cohort studies in different endemic areas.

In an earlier phase of this project, a single allele PfAMA1 FVO [25-545] was produced under current Good Manufacturing Practice (cGMP) (See Faber et al. Vaccine 2008.08.55). The product was subsequently clinically evaluated in a phase I with three different adjuvants: alhydrogel, GSK's AS02A and Montanide ISA720. The results obtained were very promising, with average growth inhibition levels of up to 50% in the higher dosages AS02A and Montanide ISA720 (See Roestenberg, Plos One 2008).

One of the conclusions of this clinical trial was that the polymorphism in the PfAMA1 protein is a feature that should be addressed for the vaccine to be highly efficacious in the field.

The limited polymorphism (bi/trimorphism) of PfAMA1 enabled the design of three artificial PfAMA1 sequences with a very high coverage of naturally occurring alleles (on average > 97%). This Diversity Covering (DiCo) approach recommended by the SAC and approved by the Board in October 2008 is expected to overcome the polymorphism found in nature and to allow a broad response to all naturally occurring AMA1 alleles. The total budget of AMA1-DiCo will be up to € 5,206,111. Both in rhesus and rabbit immunogenicity studies this expectation has been met.

CSVAC

Partners

European Vaccine Initiative, DE
Jenner Institute, University of Oxford, UK
Royal College of Surgeons in Ireland, IE

This project was selected for funding by the SAC and approved by the Board in 2008. The project main objectives were to generate a recombinant Chimpanzee adenovirus serotype 63 (ChAd63) with a gene encoding most of the circumsporozoite protein (CSP) (full length minus Glycosyl phosphatidyl inositol (GPI) anchor sequence) and a recombinant Modified Vaccinia Ankara Virus (MVA) encoding the same insert, perform Good Manufacturing Practice (GMP) production of these vaccine candidates and conduct a dose escalating phase Ia clinical trial to assess the safety and immunogenicity of ChAd63 CSP and MVA CSP in humans. Process development and GMP production are supervised by UOXF and the

phase I clinical trial will be conducted at RCSI. UOXF will act as sponsor of the phase Ia clinical trial. The total budget of CSVAC is € 1,161,000

The CSP is an attractive antigen because four efficacy trials in humans have demonstrated that two vaccines, RTS,S/AS02A and RTS,S/AS02D, which use this antigen alone can partially and temporarily prevent *Plasmodium falciparum* infection and clinical malaria.

The same antigen (CSP) has been used, but with an alternative delivery system, which uses the non-replicating ChAd63 as a vector along with a heterologous MVA boost. This new vaccine could also, in later clinical trials, be combined in a sequence with the current RTS,S/AS02D, which might produce stronger or more lasting immunity. Alternatively, and more readily, it could be combined with other ChAd63 and MVA vectors encoding mulltiple epitope-thrombospondin-related adhesion protein (ME-TRAP), Merozoite Surface Protein (MSP1) and AMA1 being developed with support from the European Commission funded European Malaria Vaccine Development Association (EMVDA), the Medical Research Council (MRC), the Wellcome Trust and other funders.

The use of viral vectors rather than or in addition to a protein adjuvant vaccine has several well recognised advantages. In pre-clinical and clinical studies the T cell immunogenicity of viral vectors consistently exceeds that of protein/adjuvant vaccines, both for induction of effector T cell and memory T cell responses. In pre-clinical models of malaria there is extensive evidence that T cells against the liver- stage parasite induce protective immunity. However, it is also clear that high level antibodies against the central repeat of the CSP are protective in small animal models. Moreover, analysis of the immunological correlates of immunity induced by the RTS,S/AS02 vaccine in both phase IIa sporozoite challenge studies and in a recent clinical trial in Mozambique provide evidence that very high levels of antibodies correlate with protection in humans. However, this correlation is relatively weak and there may be a component of T cell mediated protection induced by the vaccine, even though the magnitude of the T cell response measured after vaccination is modest, a level of about 150 SFU / million Peripheral Blood Mononuclear Cells (PBMCs) on Enzyme Linked Immuno Spot Assay (ELISpot).

GMZ2

Partners

European Vaccine Initiative, DE
African Malaria Network Trust, TZ
Albert Schweitzer Hospital, GA
Centre National de Recherche et de Formation sur le Paludisme, BF
Henogen (now novasep), BE
Makerere University, UG
Medical Research Council, GM
Navrongo Health Reseach Centre, GH
Statens Serum Institut, DK
University of Tübingen, DE

The discovery of GLURP and MSP3 was based on the *in vitro* analysis of the passive transfer of clinical immunity by purified African Immunoglobulin G (Druihle et al. 1997, Sabchareon et al. 1991). These investigations have led to the elucidation of a putative effector mechanism in the defense against *Plamosdium falciparum* malaria, and the subsequent identification of the involved parasite molecules. The studies lead to the identification of the N-terminal region of GLURP (GLURP27-489) and the C-terminal region of MSP3, (MSP3210-380) (Oeuvray et al. 1994) as targets of biologically active antibodies.

Immuno-epidemiological investigations have confirmed the relevance of anti-GLURP and anti-MSP3 IgG antibodies to acquired protection: For GLURP, several independent studies performed in geographically different locations in Africa and Asia have demonstrated a statistically significant correlation between levels of GLURP-specific IgG3 and/or IgG1 antibodies and clinical protection against malaria. This association is highly significant and the significance is confirmed after controlling for the confounding effect of age-related increase in exposure to *Plasmodium falciparum*. These results confirmed previous studies, which found that naturally occurring IgG antibodies to GLURP are associated with protection against disease in Gambian children and against high levels of parasitemia in children from Liberia and Burkina Faso. For MSP3, a high ratio (> 2) of cytophilic to non-cytophilic antibodies (IgG1 + IgG3 / IgG2+IgG4+IgM) allows distinguishing individuals without recorded malaria attacks from individuals with recorded malaria attacks. This difference is found in every age group among approximately 200 villagers from Dielmo who have been under daily clinical surveillance for more then eight years. Sequence analyses of the $GLURP_{27\text{-}489}$ and $MSP3_{210\text{-}380}$ regions from 44 field isolates and laboratory lines of *Plasmodium falciparum* show that defined epitopes in GLURP (P1, P3, and P4) (42) and MSP3 (b peptide) (30)which are targeted by Antibody Dependent Cellular Inhibition ADCI-effective human antibodies are almost completely conserved, suggesting that they are functionally constrained and not subject to selection for variation at the amino acid level. Of the different epitopes in the $GLURP_{27\text{-}489}$ region, P3 might be the most important, since

affinity-purified human antibodies against the P3 peptide mediate the strongest ADCI-effect *in vitro*.

Two phase I clinical trials have been performed with the individual GLURP and MSP3 antigens as long synthetic peptides EMVI. Both vaccines induced strong humoral and cellular responses in the volunteers, and the antisera could act synergistically with human blood monocytes to inhibit *Plasmodium falciparum* growth *in* vitro) (Hermsen et al. 2007). Further, a GLURP-MSP3 hybrid protein (GMZ2) malaria vaccine has been evaluated in phase I clinical trials in Europe and African adults (EMVI).

JAIVAC-1

Partners
European Vaccine Initiative, DE International
Centre for Genetic Engineering and Biotechnology, IN
Bharat Biotech, IN
DiagnoSearch Life Sciences Pvt. Ltd., IN
European Vaccine Initiative, DE
Intox Pvt. Ltd, IN
Lotus Labs. Pvt. Ltd., IN
Malaria Vaccine Development Program, IN

This project was selected for funding by the SAC and approved by the Board in 2003. The overall aim of this project is to develop and produce under current Good Manufacturing Practice (cGMP) conditions a bivalent malaria blood stage vaccine candidate, and to assess safety and immunogenicity in phase I clinical trial.

An effective vaccine is likely to require the combination of multiple *Plasmodium falciparum* antigens. The leading candidates for development of blood-stage malaria vaccines include merozoite surface proteins such as PfMSP-1, PfMSP-2, PfMSP-4 and PfMSP-5, rhoptry proteins such as PfAMA-1, PfRAP-1 and PfRAP-2, and microneme proteins such as PfEBA-175. These proteins play important functional roles in red cell invasion by *Plasmodium falciparum* merozoites. Therefore the International Centre for Genetic Engineering and Biotechnology (ICGEB) in New Delhi has developed a recombinant combination vaccine candidate, JAIVAC-1, based on two blood-stage *Plasmodium falciparum* antigens produced in *E. coli.* JAIVAC-1 is composed of a physical mixture of two recombinant proteins, namely, PfMSP-1_{19}, the 19 kD conserved, C-terminal region of PfMSP-1, and PfF2, the conserved, Duffy-Binding- Like (DBL) receptor-binding domain of PfEBA-175. Both PfMSP-1_{19} and PfEBA- 175 play distinct yet significant functional roles in red cell invasion by *Plasmodium falciparum* merozoites. It is therefore inferred that antibodies directed against their functional regions may have a synergistic effect and block

invasion efficiently thus providing significant protection against *Plasmodium falciparum* malaria.

This €1,573,313 project is co-funded by EVI and the Indian Government.

P27A

Partners
European Vaccine Initiative, DE International
ALMAC Sciences, UK
CiToxLAB, FR
European Vaccine Initiative, DE
Gregory Fryer Associates Ltd, UK
Infectious Diseases Research Institute, USA
Nova Laboratories, Ltd, UK
Output Pharma, DE
University of Lausanne, CH

Preclinical validation of the vaccine potential of P27A, an intrinsically unstructured, 104-amino acid long hydrophilic fragment of the *Plasmodium falciparum* malaria protein PFF0165c (Olugbile S. et al., Infection and Immunity), submitted in 2007 by Professor Giampietro Corradin of the University of Lausanne (UNIL), was not originally recommended for funding by the Scientific Advisory Committee (SAC). However, in accordance with a Board decision to help improve certain proposals, a six month contract was signed with UNIL in September 2008 for the evaluation of the malaria vaccine potential of P27A with various adjuvants, and a successful proposal was submitted in response to the call in December 2008. The total budget of P27A is € 1,385,450

In the search for novel vaccine candidates through genome mining, both inhibition of merozoite invasion and monocyte triggering by antibodies in Antibody Dependent Cell-mediated Inhibition (ADCI) were investigated, using first, naturally occurring antibodies in individuals with acquired protection through exposure to the malaria parasite, and later on, antibodies induced by immunisation with the various constructs studied. From a series of 95 polypeptides corresponding to 95 novel unexplored *Plasmodium falciparum* alpha helical coiled coil segments of malaria blood stage proteins, the screening process focused on 18 such novel antigenic genes, i.e. recognised by antibodies in exposed populations. Affinity purified antibodies studied in both Growth Inhibition Assay (GIA) and ADCI assays revealed that antibodies specific to 11 peptides totally or partially interrupted the intra-erythrocytic development of *Plasmodium falciparum* solely in cooperation with blood monocytes. No direct effect was observed (Villard et al., 2007).

These results are in agreement with passive transfer experiments that showed that total immunoglobulin from protected individuals passively transferred in naïve recipients were effective mainly through a monocyte-dependent, antibody-mediated effect. Selection of the vaccine candidate proposed here resulted from a series of successive screens that highlighted P27A as target of an immune response with satisfactory characteristics for vaccine development (Olugbile et al., 2009).

EC funded Projects

EMVDA: European Malaria Vaccine Development Association

Partners

European Vaccine Initiative, DE
African Malaria Network Trust, TZ
Biomedical Primate Research Centre, NL
Centre Hospitalier Universitaire Vaudois, CH
European Vaccine Initiative, DEEberhard-Karls Universität Tübingen, DE
Etna Biotech, IT
National Institute for Medical Research, UK
Pevion Biotech, CH
Radboud University Nijmegen Medical Centre, NL
Ruprecht-Karls-Universität Heidelberg, DE
Statens Serum Institut, DK
Stockholm University, SE
Swiss Tropical Institute, CH
University of Edinburgh, UK
University of Oxford, UK

The European Malaria Vaccine Development Association (EMVDA) is an Integrated Project funded under the EC's Sixth Framework Programme (FP6), and coordinated by the EVI. The project duration is five and a half year, and was initiated in December 2006 with an overall budget of €13,500,000. The overall objective of EMVDA is to support the development of vaccines that protect against *Plasmodium falciparum* malaria in endemic areas.

EMVDA seeks to deliver progress in one specific area of the European Commission's policy initiative: that of developing a malaria vaccine to reduce the global burden of malaria. EMVDA provides the resources of its membership of leading European research laboratories to bring innovative elements into the structure and exploit new facilities to develop compare and test vaccine candidates for proof of concept. It joins this effort to African efforts to obtain and deploy a malaria vaccine. As an integral part of the malaria vaccine research and development process, EMVDA offers research partnerships and training to African scientists.

IDEA: Dissecting the Immunological Interplay between Poverty Related Diseases and Helminth infections: An African-European Research Initiative

Partners

Academisch Medisch Centrum bij de Universiteit van Amsterdam, NLAcademisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum, NL
Agence Nationale de Recherches Sur Le Sida et les Hépatites Virales, FRThe Chancellor, Masters and Scholars of the University of Oxford, UK
Swiss Tropical Institute,CH
Eberhard Karls Universitaet Tübingen, DE
European Vaccine Initiative, DE
Eurovacc Foundation, NL
Ecole Polytechnique Federale de Lausanne, CH
Fondation international de l'Hopital de Dr. Albert Schweitzer de Lambarene, GB
Kenya Medical Research Institute,KE
London School of Hygiene and Tropical Medicine, UK
Ludwig-Maximilians-Universitaet München, DE
Malaria Consortium LBG, UK
Medical Research Council on behalf of its MRC/UVRI Uganda Research Unit on AIDS, UK
Institut National de la Sante et de la Recherche Medicale, FR
Istituto Nazionale Malattie Infettive L.Spallanzani – IRCCS, IT
Ifakara Health Institute, TZ
National Institute for Medical Research - Mbeya Medical Research Program,TZ
University of Ibadan, NI

Only recently it has become widely appreciated that other infectious diseases, the so called Neglected Infectious Diseases (NIDs), represent a major public health burden with a particularly great impact related to their widespread distribution across most developing countries. NIDs are caused by a large variety of infectious agents and predominantly by different types of worms. Worms are highly prevalent in tropical regions. Although most infections are asymptomatic, heavy infections result in significant morbidity. Despite limited evidence for the intervention, recent years have seen significant scale-up of population-based national programmes for integrated control of worms, following concerted advocacy and major philanthropic donations. These programmes raise important research questions about the public health implications of co-infection and treatment for other diseases such as malaria, Human Immunodeficiency Virus (HIV) and tuberculosis (TB) (Eziefula 2008). Indeed there is growing epidemiological evidence for interactions between worms and these diseases. The most recent estimates indicate that about two billion people are infected with worms corresponding to a large proportion of the world's population. Three hundred million people are severely affected and about 50% of cases are children. The worm infections include schistosomiasis and several species of intestinal worms also known as

soil-transmitted helminths. WHO estimates that about 200,000 deaths every year are caused by schistosomiasis alone (http://www.who.int/en/).

Given the wide geographic overlap in occurrence, co-infections between worms and HIV, TB and malaria occur in tens of millions of people and in both children and adults. In this regard, preliminary epidemiological data generated from a small number of studies indicated that about 25% of individuals affected by HIV, malaria or helminth infections were co-infected. Although worm infections and HIV, TB and malaria have been extensively investigated, only recently there has been increased attention to the potential impact of co-infections between worms and HIV, TB and malaria. Firstly, the interaction between these diseases has potential major public health implications by increasing the diseases burden since effective vaccines are not yet available for these infections. Secondly, although the worm, HIV, TB and malaria-specific immune responses have been the target of extensive investigation, the precise immune correlates of protection remain unknown for all these diseases. Thirdly, there is no information on whether worm-induced immunity modulates HIV-, TB- and malaria-specific immune responses. Fourthly, there is limited knowledge of the influence of underlying worm infections on the clinical course of HIV, TB and malaria. Finally, the impact of worm infections on vaccination requires further investigation as very limited data suggest reduced effectiveness of vaccines in subjects with worm infections.

The African-European Research Initiative on Co-infections of Related and Neglected Infectious Diseases (IDEA) is a five year project with twenty consortium members coordinated by Centre Hospitalier Universitaire Vaudois, University of Lausanne and has a total budget of €10,300,000.

INYVAX: Optimisation of the development of Poverty-Related-Diseases (PRD) vaccines by a transversal approach, addressing common gaps and challenges

Partners

European Vaccine Initiative , DE
Biomedical Primate Research Center, NL
Brighton Collaboration Foundation, CH
Fondation Mérieux, FR
PATH Malaria Vaccine Initiative, USA
TuBerculosis Vaccine Initiative, NL
Université de Genève, CH
World Health Organization, CH

A number of new vaccines are being developed against poverty-related infectious diseases of major global public health importance.

The development of these vaccines is facing the same kinds of challenges and gaps, which still prevent the following:

1. Establishment of readily accessible formulation and scale-up process development capacity for neglected disease vaccines;
2. Establishment of a systematic approach for prioritising formulation of vaccine candidates using accepted preclinical criteria;
3. Development of information-sharing tools to strengthen connections between scientists, developers and clinical investigators.

These challenges include difficulties in accessing know-how and technology platforms in vaccine development, formulation and delivery, difficulties in harmonising safety data collection, and an insufficient number of trained scientists able to undertake leadership roles in vaccine development.

The Optimisation of the Development of Poverty Related Diseases Vaccines by a Transversal Approach, Addressing Common Gaps and Challenges (INYVAX) is a €932,335, three year project funded under EC's FP7 coordinated by EVI. The project started in 2009.

OPTIMALVAC: Initiative on Optimizing Malaria Vaccine Lab Assays Evaluation

Partners

Barcelona Center for International Health Research, ES
Biomedical Primate Research Center, NL
Centers for Disease Control and Prevention, USA
European Vaccine Initiative, DE
Health Protection Agency/ National Institute for Biological Standards and Control, UK
ImmunoVacc Consulting, BE
Institut Pasteur, FR
PATH Malaria Vaccine Initiative, USA
Radboud University Nijmegen, NL
University of Stockholm, SE
University of Edinburgh, UK
University of Oxford, UK
World Health Organization, CH

The Initiative on Optimising Malaria Vaccine Lab Assays Evaluation (OPTIMALVAC) is a three year project funded under EC' FP7 with thirteen consortium members coordinated by EVI with a budget of €1,000,000 including complementary contributions from the Malaria Vaccine Initiative (MVI) (€561,395) and the Centres for Disease Control and Prevention (CDC) (€30,000). The Grant Agreement was signed by the EC on 7 September 2009.

A broad range of malaria vaccine candidates, derived from a diverse set of technologies, has been created from the multiple approaches being taken by different groups in developing malaria vaccines. The majority of vaccine candidates are recombinant proteins based on complex native antigens found on the surface of the parasite. The vaccine potential of these parasite surface antigens is often supported by epidemiological data, and by the ability to induce measurable antigen-specific antibodies or potential protective responses in animals, and later in humans. *In vivo* assays such as protection models in mice or non-human primates, as well as human sporozoite challenge, provide additional data for some relevant antigens (e.g. pre-erythrocytic antigens).

Individual groups have developed assays within the context of their vaccine discovery efforts, with identification of measurable processes for parasite growth and virulence to test specific antigens. In-house assays are strain-, stage- and even process-specific, and the ability to compare results between different candidates is further limited by diverse methodologies and assay components such as parasites, cells and reagents. The lack of harmonisation of malaria vaccine assays leads to scepticism about the comparability of assay results that in turn generate controversy and uncertainty about the efficacy of the vaccines.

The main goal is to harmonise the Immune Fluorescence Assay (IFA), the Antibody-dependent Cellular Inhibition (ADCI) assay, Intracellular Cytokine Staining (ICS) and Enzyme-linked Immunospot (ELISpot)) to facilitate comparison of results and improve decision making on vaccine construct development, product characterisation, down selection of vaccine candidates and/or formulations, and clinical development plans.

PHARVAT:Platform for the Harmonisation of Vaccine Adjuvant Testing

Partners
Biomedical Primate Research Centre, NL
European Vaccine Initiative, DE
World Health Organization, CH

PHARVAT is an EC FP7 funded project aiming to generate a harmonised procedure to permit pre-clinical selection of vaccine adjuvants. The project run for a two year period and was initiated in November 2009 with an overall budget of € 300,000 and ended in October 2011.

The careful selection of adjuvants is critical to the quality and magnitude of the immune response generated by a particular vaccine. At present, the tools available to allow an informed selection of superior adjuvants and/or formulations are limited and

unharmonised. The development of harmonised assays, which can provide benchmarking tools by which new formulations/adjuvants can be assessed/downselected and will allow the comparison of adjuvants/formulations across different studies, is of clear benefit. The overall objective of the PHARVAT project was therefore surveying best practices in adjuvant testing, evaluation of proposals for harmonised adjuvant testing and consultation of stakeholders as well as dissemination of the results and provision of a harmonised adjuvant testing method.

TRANSVAC: European Network of Vaccine Research and Development

Partners

Biomedical Primate Research Centre, NL
Central Veterinary Institute, NL
European Vaccine Initiative, DE
Helmholtz Zentrum für Infektionsforschung GmbH, DE
Health Protection Agency, UK
LIONEX GmbH, DE
London School of Hygiene and Tropical Medicine, UK
Max Planck Institute for Infection Biology, DE
Tuberculosis Vaccine Initiative, NL
University of Oxford, UK
University of Lausanne (WHO reference centre), CH
Vakzine Projekt Management GmbH, DE

Although expertise already exists within Europe spanning different diseases types, there is currently very limited coordination between vaccine Research and Development (R&D) groups, assay developers, and vaccine producers. Unarguably, fragmentation of expertise and facilities has slowed and in some instances distinctly impeded the development and validation of promising vaccines. To address these challenges the European vaccine development community needs to establish a collaborative vaccine development infrastructure based on shared visions and goals.

Despite Europe's significant vaccine R&D expertise, there is currently a strong need to improve cooperative efforts between R&D groups and vaccine producers across Europe. At present, any R&D group wishing to develop a new experimental vaccine needs to individually locate and approach a fragmented and non-harmonised group of vaccine development service providers.

TRANSVAC is a collaborative infrastructure project funded under the EC FP7. The program runs from October 2009 till October 2014 and has a total budget of €9,899,999. The project is the joint effort of leading European groups in the field of vaccine development, and is coordinated by the EVI. TRANSVAC was designed in order to

enhance European research and training and foster the seamless implementation of a permanent research infrastructure for early vaccine development in Europe.

TRANSVAC aims to accelerate the development of promising vaccine candidates by bridging the gap between bench research and clinical trials through the provision of expertise on e.g. antigen discovery, formulation, in vivo models and antigen production. The project will be the European driving force for vaccine development by establishing an efficient sustainable collaborative infrastructure based on a shared visions and goal.

EDCTP funded Project

MVVC: Malaria Vectored Vaccines Consortium

Partners

Centre National de Recherche et de Formation sur le Paludisme, BF
European Vaccine Initiative, DE
Kenya Medical Research Institute, KE
Medical Research Council Laboratories, GM
Okairòs srl, IT
Université Cheikh Anta Diop, SN
University of Oxford, UK
Vienna School of Clinical Research, AT

MVVC is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) in response to a Call made in 2008: Malaria Vaccines Integrated Project – Clinical Trials/Capacity Building/Networking. The total funding provided by EDCTP is € 6,500,000. This is completed by co-funding from the Irish Aid Department of Foreign Affairs, the Swedish International Development Agency (Sida), the Medical Research Council (MRC), UK and the Federal Ministry of Science and Research, Austria and third-party contributions from all the partners of the project, the total budget being € 9,500,000. The project is scheduled to last for 4 years (2009 -2013).

The MVVC consortium includes four African and four European partners with EVI as coordinator. The collaborators and partner institutions were selected based on the proposed objectives of the consortium and what expertise they and their institutions will bring collectively to the mutual benefit of all partners. UOXF is sponsor of the clinical trials and has developed and manufactured the vaccines being tested. Okairos is specialised in development and production of adenoviral vectored vaccines. VSCR provides training and coordinates courses for members of the MVVC consortium. The three of the African centres (CNRFP, KEMRI, and MRC) are experienced in the conduct of clinical trials, the fourth centre, the Université Cheikh Anta Diop (UCAD) is will set up the structure to

conduct clinical trial and provide the facilities for the conduct of the malaria vaccine clinical trials. The projects main objective is the demonstration of the safety, immunogenicity and efficacy of the malaria vaccine candidates, ChAd63 ME-TRAP + MVA ME-TRAP in adults, young children and infants in sub-Saharan Africa, by integrating capacity-building and networking in the design and conduct of phase I and II clinical trials of viral vectored candidate malaria vaccines in East and West African adults, children, and infants.

Its specific objectives are as follows:

- To conduct phase Ib clinical trials of an ChAd63 ME-TRAP vaccine, to assess safety and immunogenicity in African adults and children;
- To conduct a multi-site phase IIb trial of a prime-boost vaccine (ChAd63 ME-TRAP + MVA ME-TRAP) in African adult, for efficacy against clinical malaria;
- To conduct a multi-site phase IIb trial of a prime-boost vaccine (ChAd63 ME-TRAP + MVA ME-TRAP) in African children aged 5-17 months, for efficacy against clinical malaria;
- To build capacity so that partner sites, especially the UCAD and CNRFP, are able to conduct clinical trials to internationally recognised standards
- To facilitate activities of partners, with established networks to build clinical research capacity and with each other to deliver project-specific goals.

Preclinical, Process, Production, Investigational Medicinal Product Dossier (IMPD)

AMA1-DiCo

BPRC finalised a report in 2011 on the studies performed in mice and rabbits to identify potential novel adjuvants for use in AMA1-DiCo phase Ia/Ib Clinical Trial. Seven different adjuvants formulations were evaluated using a single allele AMA1 vaccine. From these results and in view of its sustainable availability, GLA-SE (IDRI, USA) was selected as novel adjuvant for the phase Ia/Ib clinical trial.

A potency study work plan on the AMA1-DiCo antigens has been established and outsourced at Confarma. During the year 2011, three studies aiming at generating standard mice sera, validating the Enzyme Linked Immunosorbent Assay (ELISA) protocol and assessing a dose range for the potency release study have been completed.

AMA1-DiCo Drug Substances (DS) has been manufactured under current Good Manufacturing Practice (cGMP) conditions at Fraunhofer IME. Quality Control (QC) assays, batch release and certificate of analysis of the DS have been finalised in December 2011. Several formulation studies, filling into glass vials and lyophilisation cycle development have been carried at Nova Laboratories in 2011. It is anticipated that the GMP lyophilisation run will be carried early 2012.

CSVAC

Toxicology studies were conducted from March to August 2011 at Huntingdon Life Sciences.

Process development of Chimpanzee Adenovirus 63 (ChAd63) CircumSporozoite Protein (CSP) was conducted at the Clinical Biomanufacturing Facility (CBF) University of Oxford (UOXF) from January to March 2011.

GMP production of the clinical batches of ChAd63 CSP vaccine was completed during the year at the CBF UOXF. GMP manufacturing of ChAd63 CSP was from January to May and Quality Control (QC) release from May to October 2011. The release of the Clinical batch by a Qualified Person (QP) was done in December 2011 at CBF.

The development of the Investigational Medicinal Product Dossier (IMPD) for the ChAd63 CSP and Modified Vaccinia Ankara (MVA) CSP vaccines was completed during the year 2011 under the supervision of the UOXF team.

GMZ2

Dr Theisen, SSI (DK), submitted an update on the project at the EVI SAC meeting in November 2011. The studies were mainly addressing the validation of the ADCI functional assay and the assessment of IDRI adjuvant to enhance the immune response. The continuation of EVI support will be decided in 2012.

EMVDA

ChAd63 (University of Oxford)

The selected blood stage malaria vaccines were the simian adenovirus ChAd63 and Modified Vaccinia Ankara (MVA) expressing PfMSP1 and PfAMA1. No pre-clinical activity in year 2011.

MSP1 (University of Heidelberg)

Preclinical studies on mice and rabbits using laboratory grade MSP1 and several adjuvants from Infectious Disease Research Institute (IDRI) and BTG have been carried in 2011. The adjuvant selection for the clinical phase I clinical trial will be completed early 2012. A second GMP production optimised run of the full length recombinant MSP1-1D Drug Substance (DS) was performed at Biomeva early 2011. The GMP DS batches were released in May and September 2011. The selection of a contract manufacturing organisation for the formulation, filling and lyophilisation of the drug product is deemed to be completed by early 2012. A contract research organisation for the preclinical potency and toxicity studies has been selected in December 2011. A scientific advice will be requested early 2012 to the Paul Ehrlich Institute to review the chemistry, manufacturing, control documentation part of the Investigational Medicinal Product Dossier (IMPD) as well as the preclinical package and the clinical trial design protocol.

pfPEBS (Umiversity of Lausanne)

Process development for synthesis of pfPEBS (formerly known as SR11.1) peptide took place during the second half of July 2011. In August and September the initial production runs of the SR11.1 antigen by Synprosis was performed which yielded a quality control reference batch. Further synthesis optimisation took place and the production lots for toxicological study and clinical trial have been finalised and released in October and November 2011. The clinical batches have been sent for toxicological studies to the Contract Research Organisation (CRO) Confarma on November 14th 2011.

The Investigational Medicinal Product Dossier (IMPD) has been developed in November 2011.

P27A

The P27A ELISA validation plan to assess the immunogenicity of the P27A vaccine candidate in the release toxicology study has been finalised at CiToxLAB in December 2011. The purification development of the crude P27A peptide has been completed at ALMAC Sciences. The GMP manufacture of the P27A Drug Substance (DS) has been completed and the batch was released in September 2011 by the Qualified Person (QP) at ALMAC Sciences.

Formulation studies, filling into glass vials and lyophilisation cycle development have been carried at Nova Laboratories in 2011. It is anticipated that the GMP lyophilisation run will be carried early 2012.

TRANSVAC

Preclinical, Process and Production

The research component of TRANSVAC targets the improvement of the use of (molecular) assays and standardised reagents, adjuvants, animal models and vaccine and cell bank production specific to the development of experimental vaccines. Seven of the 15 project Work Packages (WPs) in TRANSVAC are dedicated to research into these aspects of vaccine development. In 2011 the main results were obtained:

- *Production of recombinant vaccine candidate*

  Two antigens (Ag85A and MSP1-FusN) were selected and the target gene synthesised and expressed in *E. coli*. For both antigens a purification process for future Good Manufacturing Practice (GMP) production could be established. In addition, eight more antigens have been purified in bulk and were made available i.e. ESAT6 (Rv3875), CFP10 (Rv3874), 19 kDa (Rv3763), PncA (Rv2043c), HSP70 (Rv0350), HSP65 (Rv0440), Antigen 85B (Rv1886c), and Antigen 85C (Rv0129c). The antigens are also available to outside users, taking into consideration that the activities of this WP are not access but research activities.

- *Evaluation of vaccine candidates in different animal models*

Protocols for evaluation of (multiple) cytokine responses in mice, pigs and Non-Human Primates (NHP) for future vaccine candidate evaluation were established and/or expanded. Sufficient material from guinea pigs was stored and PCR primers for selected biomarkers for use in guinea pigs for further vaccine evaluation were established.

It was determined that immune responses in very young versus (sub-) adult pigs show remarkable differences in immune responses against influenza vaccination. Protocols for isolation of cells in NHP studies have been produced.

- *Definition of biomarkers of protective immunity through global analyses of host responses after vaccination*

  As an agreed vaccine candidate, BCG samples of a clinical phase Ia clinical trial (sex and age matched European (Caucasian) males, 25-35 years naïve and BCG vaccinated clinical trial participants, performed in Germany), were made available through Vakzine Projekt Management (VPM). Total RNA was isolated from agreed samples at Max Planck Institute followed by Bioanalyser Quality Control (QC) measurement and Nanodrop quantification. Aliquots of total RNA and relevant sample information were collated and shipped to the partners Helmholz Institute and LIONEX. Analysis of these samples is currently in progress.

- *Harmonisation of immuno-assays for clinical trials*

  Assay harmonisation and qualification of the three main technologies: Intracellular Staining (ICS), ELIspot, antigen specific IFNγ ELISA is underway. The Standard Operating Procedures (SOPs) and protocols have been exchanged and a first stage assay harmonisation process has been completed.

  An intracellular flow cytometry standard is already available. A cell-based ELISpot reference preparation is in the early stages of development. Antigen 85a was supplied by partner VPM and a test fill was performed using four different formulations and cycling conditions used in a previous trial. Other formulations will be used in other test fills to establish an appropriate formulation without albumin.

Transnational Access Services

The TRANSVAC Scientific Advisory Committee (SAC) and User Selection Panel (USP) have completed evaluation of applications received in response to the TRANSVAC

transnational access services call during 2011. A total of 11 user project has been selected in 2011 and have been given access to following services:

- Experimental Non-human primate model facility, Biomedical Primate Research Centre, The Netherlands
- ILLUMINA Deep Sequencing, Helmholtz Centre for Infection Research, Germany
- Vaccine formulation laboratory, World Health Organization Collaborating Centre - University of Lausanne, Switzerland
- AGILENT Microarrays, Max Planck Institute for Infection Biology, Germany
- Large Animal studies, Central Veterinary Institute of Wageningen, The Netherlands
- Experimental murine validation platform, Helmholtz Centre for Infection Research, Germany
- ILLUMINA Deep Sequencing, Helmholtz Centre for Infection Research, Germany

The deadlines for the different calls are available at http://www.transvac.org/open-call.

Delivery Platforms, adjuvants and viral vectors

EVI has purchased, under a material transfer agreement, Good Manufacturing Practice (GMP) -grade Glucopyranosyl Lipid Adjuvant Stable Emulsion and Stable Emulsion from IDRI for toxicology studies and is currently negotiating the transfer agreement to use the adjuvant in clinical studies.

EVI has also filled 5,000 vials of 0.6ml of Aluminium Hydroxyde under GMP conditions at Serum Institute of India to be used in all its preclinical and clinical trials.

AMA1-DiCo

GLA-SE and Aluminium Hydroxyde as a comparator, will be used as adjuvants in the phase Ia/Ib clinical trial.

CSVAC

The malaria antigen, Circumsporozoite Protein (CSP) is delivered in a prime boost strategy by two different vectors, Adenovirus (ChAd63) and Modified Vaccinia Ankra (MVA).

GMZ2

Aluminium Hydroxide is the reference adjuvant currently being used in all the proposed clinical trials of GMZ2. GMZ2 is expressed in *Lactococcus lactis*.

JAIVAC

The adjuvant selection involved Aluminium Hydroxyde, AS02A, Montanide ISA 51 and Montanide ISA 720. Based on the immunogenicity as assessed by ELISA, Immunofluorescence assay (IFA) and parasite growth inhibition data, it was recommended that Montanide ISA 720 be considered for further clinical development. JAIVAC-1 is expressed in *E. coli*.

P27A

Two adjuvants will be used in the clinical trials: Aluminium Hydroxyde as a reference adjuvant but also because it has shown good results in preclinical studies and GLA-SE from IDRI.

PHARVAT

A survey on adjuvant practices was disseminated at the Modern Adjuvant / Vaccine Formulation (MAVF) Conference in Cannes, October 2010, which was attended by major stakeholders from industry as well as from public research organisations. The questionnaire was designed such that an overview would be obtained on methods currently in use in adjuvant testing. It also included a number of questions on a proposed harmonised adjuvant evaluation method. From the questionnaire it was evident than no two respondents used similar methods for adjuvant comparisons. Evaluation of adjuvant activity was mainly done in mice, but that was one of the few consensus points. A plethora of mice lines, immunisation schedules, dosages and route of immunisation was listed. Based on the questionnaire outcomes, an analysis of the literature, and the personal expertise of the PHARVAT members it became clear that there is no 'best' evaluation method, but that there is a need for a method and protocol to be chosen and used as the harmonised method. Therefore a harmonised adjuvant comparison method was proposed. It was decided to provide reference antigens, together with a protocol for the use thereof as well as reference sera.

Three antigens were selected:

1. Apical membrane antigen 1 (AMA1) from *Plasmodium falciparum*. This is a malaria vaccine candidate aiming at inducing humoral (antibody responses),
2. Antigen 85A from *Mycobacterium tuberculosis*, a tuberculosis (TB) vaccine candidate eliciting (well characterised) cellular responses, and
3. Hepatitis B surface antigen (HBsAg) as a model for a particulate antigen that induces both cellular and humoral responses.

All three antigens are available in Good Manufacturing Practice (GMP) grade and in sufficient quantities to allow for distribution.

Three reference adjuvants were selected:

1. Aluminium Hydroxide as first reference because it is the most widely used class of adjuvant and as such serves as a baseline reference,
2. Squalene Oil in Water, a more novel formulation that has been used in humans (e.g. pandemic influenza), and
3. A liposomal formulation with the Saponin Quillaja saponaria 21 (QS21).

The availability of the antigens has been arranged, with AMA1 being made available by BPRC, Ag85A through LIONEX and HBsAg through WHO. The antisera generated will be made available through a repository set up at the WHO. The sera thus generated will be assigned an amount of arbitrary PHARVAT units and will be included in an adjuvant reference kit. The results from the mouse study will be published in a peer reviewed journal and all methods and procedures will be documented in SOPs that will be made available through the PHARVAT website.

The paper will describe the rationale behind the harmonised method as well as the formulation of the antigens with adjuvant to produce the vaccines used vaccine and the immunological outcomes.

Together this will constitute a reference for future adjuvant comparisons. This is further facilitated by the availability of the antigens and reference sera through the repository set up at the WHO. The adjuvants can be obtained from the Vaccine Formulation Laboratory (VFL) at University of Lausanne. The high-titered reference sera generated in the PHARVAT project should suffice for at least 20,000 tests per antigen and will as such be a valuable reference for adjuvant comparisons.

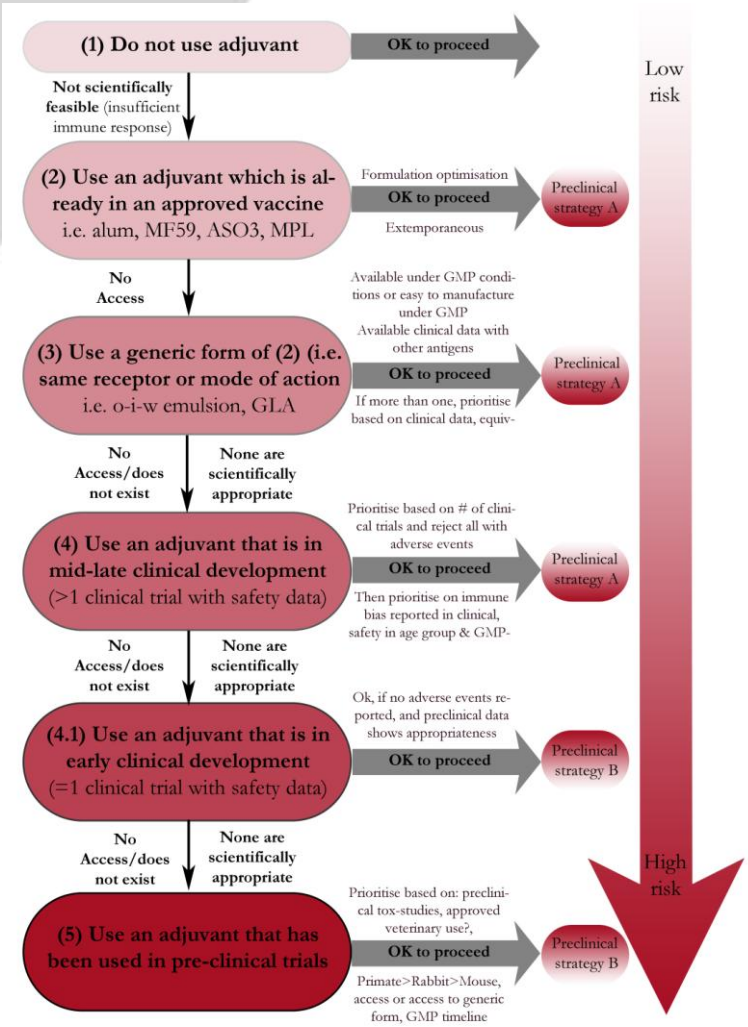
INYVAX

Most research on new vaccines such as malaria, Human Immunodefiency Virus (HIV) and tuberculosis (TB), has not been performed using appropriate adjuvants or formulations. This is particularly true where research and development has been undertaken in the public or small biotech sector. There is therefore a need to ensure the availability of potent adjuvants to the public research sector to facilitate the development of effective vaccines against diseases for which we do not yet have vaccines and also to improve vaccines such as influenza, TB, etc. With INYVAX support, the Initiative for Vaccine Research (IVR) at the World Health Organization (WHO) has strengthen the Global Adjuvant Development Initiative (GADI), and WHO has also extended the Adjunet network to Europe.

Antigens, adjuvants and standard sera and harmonised protocol will constitute the "Adjuvant evaluation" kit that will enable harmonised testing of adjuvants . The kit is available at upon request at Vaccine Formulation Laboratory

The INYVAX rules for decision making in formulating the vaccines with adjuvant are extremely useful to advice scientists on how they should approached the challenge of optimising immunogenicity of their antigens; (see fig 1).

Figure 1: INYVAX decision making tree for formulating vaccines with adjuvant



TRANSVAC

Coherent development of novel and improved vaccine formulations

Two antigens (AMA1 and Antigen 85A (Ag85A)) and three adjuvants (Aluminium Hydroxyde, a squalene in water emulsion (SWE) and a liposome-QS21 (Lip-QS21) formulation) were selected. Standard Operating Procedures (SOPs) were drafted, preliminary stability data was generated and several Quality Control (QC) tests were performed.

Development of cell line substrates for the production of viral vaccines

To develop a widely accessible bank of cell lines suitable for Good Manufacturing Practice (GMP) manufacture of viral vectored vaccines, particularly adenoviruses and poxviruses, three available cell lines were selected:

- A low passage HEK293 cell line

- A VERO cell line from the WHO bank
- 911 Cells from Prof Rob Houben from the Leiden University Medical Centre

From these cell lines Master Cell Banks (MCB) were produced by the University of Oxford's Clinical Biomanufacturing Facility. These MCBs are suitable substrates for (pre-) GMP production of vaccine candidates.

Transnational Access Services

The TRANSVAC Scientific Advisory Committee (SAC) and User Selection Panel (USP) have completed evaluation of applications received in response to the TRANSVAC transnational access services call during 2011. A total of 11 user project has been selected in 2011 and have been given access to following services: High in demand where the services provided by the Vaccine formulation laboratory at the World Health Organization Collaborating Centre (University of Lausanne, Switzerland)

CLINICAL DEVELOPMENT

SELECTION OF SPONSORS AND CLINICAL TRIAL CENTRES FOR PHASE I CLINICAL TRIALS

EVI has conducted the selection of a clinical trial sponsor for several core projects. The selection process included multiple potential sponsor sites. After a first selection based on capacities and costs, an audit was performed at three sites by an external auditor and a member of EVI. The selection of a sponsor was based on the audit results and was further recommended by the EVI SAC and approved by the EVI Board.

AMA1-DICO

During 2011, the clinical development plan has been prepared. The same clinical strategy as the P27A project of combining phase Ia and phase Ib arms in an unique protocol has been taken. In summary, the clinical phase Ia/Ib will be staggered, randomised, single-blind, multi-centre trial.

The objectives of the clinical trial will be to evaluate the safety and the immunogenicity of 50 µg AMA1-DiCo malaria vaccine candidate with GLA-SE and Aluminium Hydroxide as adjuvant, in healthy adults not previously exposed to the parasite *Plasmodium falciparum* living in Europe and in healthy African adults exposed to the parasite.

The selection of the investigational sites in Europe and in Africa, the laboratories which will conduct the safety and immunogenicity clinical trial and the finalisation of the protocol synopsis will be carried out in 2012. The phase Ia/Ib AMA1-DiCo clinical trial is scheduled to start in 2012.

CSVAC

A clinical trial funding contract was signed between EVI and the Royal College of Surgeons in Ireland (RCSI) in Q3 2011. All Regulatory Authorities (MHRA UK and IMB, Ireland) and institutional Ethics Committee approvals for the clinical trial were obtained from University of Oxford (UOXF) and RCSI respectively. A clinical trial site evaluation of RCSI was completed in Q3 2011 by an EVI team which included an independent auditor. A site initiation visit of RCSI was conducted in December 2011 by an independent clinical trial monitor appointed by the sponsor. Recruitment of subjects for the phase Ia clinical trial has reached an advanced stage. First vaccinations of subjects in the phase Ia clinical trial at RCSI is expected to commence early in Q1 2012.

EMVDA

EMVDA ChAd63: The vaccine candidates under evaluation are the simian adenovirus 63 (ChAd63) and modified vaccinia virus Ankara (MVA) expressing PfMSP1 and PfAMA1. The phase I/IIa clinical trial which commenced in Q3 2010 was completed in July 2011. The vaccines were safe and immunogenic. Post-challenge follow-up of volunteers in the phase IIa efficacy study (human sporozoite challenge) of these vaccines was completed during the year.

EMVDA pfPEBS: In the summer of 2011 the principal investigator and the inventor Dr Francois Spertini, Centre Hospitalier Universitaire Vaudois, and Dr Pierre Druilhe, Vac4All, respectively, started to examine in details some of the more critical steps of the manufacturing and mostly of the Clinical Trial Plan (CTP), including immunoanalysis. A general meeting was held in Lausanne in September 2011 to review the main critical steps and finalise the last decisions required both for clinical work, laboratory work and ethical as well as regulatory matters. The Clinical Trial Application (CTA) and Investigational Medicinal Product Dossier (IMPD) have been submitted in November 2011. The expected outcome of the four to six weeks review by the Institutional Review Board (IRB) plus the four to six weeks review by Swiss Medic will merge with the report from the toxicological studies at Confarma. This will lead to a recruitment that will start as soon as the IRB has given its agreement, most likely early January 2012, and will lead to a first administrations by mid-February 2012.

P27A

During the year 2011, the clinical development plan was prepared. The project team proposed to design the clinical phase I clinical trial as a staggered, randomised, single-blind, multi-centre trial, including in the same protocol phase Ia and phase Ib arms. The objectives are the assessment of the safety and the immunogenicity of 50 μg P27A malaria vaccine candidate with a lower and higher dose of GLA-SE and Aluminium Hydroxide as adjuvant, in healthy adults not previously exposed to the parasite *Plasmodium falciparum* living in Europe and in healthy African adults exposed to the parasite.

After reviewing the sponsor contract, the selected sponsor for the P27A clinical trial has declined to take the sponsor responsibilities but has nonetheless proposed to perform the clinical trial management. EVI has therefore identified another sponsor that is willing to take the sponsor responsibilities. An audit of the sponsor site has been conducted by an

external auditor and the quality assurance manager of EVI that has led to a positive outcome. It is anticipated that the contract with the sponsor will be finalised early 2012. The phase Ia/Ib P27A clinical trial is scheduled to start in 2012.

GMZ2

The EDCTP funded multi-centric phase IIb clinical trial of the GMZ2 malaria vaccine candidate continued into 2011 with the vaccine develop and manufactured through EVI funding. The investigational sites which continued to recruit children included the Iganga site, Makerere University, Uganda, Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso and Navrongo Health Research Centre (NHRC), Ghana. In 2011, follow-up of subjects continued at Albert Schweitzer Hospital (ASH) Lambaréné, Gabon and at the three investigational sites mentioned above. Results of the multi-centre phase IIb clinical trial are expected in Q2/Q3 2012.

JAIVAC-1

The administration of vaccines in the phase Ia dose escalation clinical trial which started in Q3 2010, continued during the year 2011. A total of 45 young adults received two doses of vaccine, and where followed for safety and immunogenicity one year after the first dose, except for one subject who had to withdraw his consent as he moved away from the Bengaluru. . No Serious Adverse Events were reported. The independent Data Safety Monitoring Board (DSMB) did not raised any safety concerns. Interim Analysis of safety and immunogenicity (ELISA and ImmunoFluorescence Assay (IFA) one month after the booster administration) has been completed.

ELISA results indicate that PfF2 was immunogenic with significantly higher antibody titres at the higher doses (25 and 50 compared to 10 micrograms). However, immune responses generated by *Pf*MSP1-19 were not supporting the continuation of the project. An integrated clinical study report is being compiled. A manuscript for publication in a peer-review journal will be submitted during 2012

The clinical audit of Lotus Labs, DiagnoSearch Life Sciences, International Centre for Genetic Engineering and Biotechnology (ICGEB) and Malaria Vaccine Development Programme (MVDP) was conducted by Rita Walt (RW Consulting GmbH) and Nathalie Imbault (EVI) in Q4 2011.

IDEA

The IDEA work package (WP) on the assessment of the intestinal helminth infections on the immune response of tuberculosis (TB), Malaria, and Human Immunosuppressive Virus (HIV) vaccine is co-lead by University of Oxford and EVI, and the activities commenced in April 2011. The process of obtaining consensus, approvals and signing of agreements with clinical trial principal investigator's (PI) for add on worm studies to malaria, TB and HIV clinical trials in Africa is on-going. Independent Ethics Committee and Regulatory Authority approval was obtained for add-on studies for malaria vaccine trials in Lambarene, Gabon. This clinical trial is on-going. There has been some difficulties with adding on studies to on-going clinical trials for TB and HIV especially with the selection of TB investigational site. Challenges are mainly with the timing of clinical trials in relation to the IDEA project milestones and reporting as well as the low prevalence of worm infections in the chosen clinical trial population.

MVVC

The phase Ib clinical trial in adults which commenced in Q2 2010 at MRC Gambia and KEMRI were completed during the year 2011. The safety profile of the vaccines was acceptable at both sites and good immunogenicity data were obtained. The phase Ib clinical trial in children aged 2-6 years and 5-17 months commenced at MRC Gambia in January 2011 and October 2011 respectively. Follow-up of subjects is on-going for both clinical trials. The vaccines were safe and highly immunogenic.

Recruitment and follow-up of subjects enrolled in the baseline epidemiological studies at UCAD and CNRFP in Q4 2011 continued during the year. All recruitment targets have been met at both sites.

CAPACITY BUILDING, WORKSHOPS, TRAINING

CAPACITY BUILDING

AMA1-DiCo

Kwadwo Asamoah Kusi finalised his PhD entitled: *Towards a blood stage malaria vaccine; dealing with allelic polymorphism in the vaccine* at the BPRC in 2011. The work in described in this thesis was co-funded by EMVI/EVI.

JAIVAC

The main achievement in 2011 was the support of International Centre for Genetic Engineering and Biotechnology (ICGEB) through the JAIVAC grant for setting up of a Good Clinical Laboratory Practice (GCLP) Laboratory for the immunogenicity testing. DiagnoSearch Life Sciences (DLS), an India Contract Research Organisation (CRO) with its own GCLP Laboratory accredited by College of American Pathologist (CAP) started by an assessment of the status of the ICGEB laboratory and made recommendations. DLS did train ICGEB team in Good Laboratory Practice (GLP) and support ICGEB in setting up of the Quality Assurance system by several on site visits to evaluate the progress made. This close collaboration between these two Indian laboratories has allowed ICGEB to run GCLP Enzyme Link ImmunoSorbent Assay (ELISA) testing. Furthermore, the ICGEB team has been trained on GCLP and Good Clinical Practice (GCP) by Rita Walt Consulting.

MMVC

At Centre National de Recherche et de Formation sur le Paludisme (CNRFP), the site infrastructure and laboratory equipment upgrade has been completed at the Banfora site. At Universite Cheikh Anta Diop (UCAD), most of the work has been completed at the research site in Keur Socé. Both sites are now functioning effectively.

TRAINING

CSVAC

In 2011 there were a number of staff exchange visits between Dublin and Oxford related to CSVAC Project. A clinical trial investigator at Royal College of Surgeons in Ireland (RCSI) Dublin went to the Jenner Institute, Universty of Oxford for three weeks for training in cellular immunology, and for clinical trial specific training. A study nurse, and a

internal monitor, also spent two days in the Jenner Institute in Oxford for clinical trial specific training.

IDEA

Significant effort has been made towards harmonisation of immunological assays and diagnostic methods across the sites. Workshops have been held on PCR Diagnosis of Helminth and Malaria and on Gene Profiling Analysis. Two immunology short courses jointly funded by the Wellcome Trust also took place at Uganda Virus Research Institute in September 2011. Multiple North-South and South-South exchanges have taken place. Seven PhD fellowships have been awarded at four African institutions.

INYVAX

INYVAX has been involved in supporting and also developing several training programs for both European and low income vaccine developers. A training program on oil/water emulsion preparation and use was established and was given to the first round of trainees in March at Biofarma in Indonesia. A general training program on vaccine formulation with adjuvants has been prepared. The first course will take place January 2012. This will be conducted by the TRANSVAC consortium. INYVAX has also continued its support of students attending the Advanced Training in Vaccinology (ADVAC) course at Fondation Mérieux. The annual ADVAC course for scientists in relation to PRD vaccines took place in May at the Fondation Mérieux conference centre. Amongst the 65 participants, thirteen students were sponsored by INYVAX.

MMVC

Several workshops and trainings were successfully conducted within the MVVC project in 2011:

- Introduction to Clinical Research, Burkina Faso, 24 – 25 February
- Introduction to Clinical Research, Senegal, 28 February – 1 March
- UCAD hosted a PhD students workshop on statistical tools, Senegal, 21 – 22 July
- UCAD hosted a finance managers workshop, Senegal, 06 – 07 September
- An applying Good Clinical Practice (GCP) course was organised by VSCR at MRC Gambia with participants of MRC Gambia, KEMRI and CNRFP. in the The Gambia

WORKSHOPS

EMVDA

A workshop took place in Amsterdam on 22 - 23 June with the following programme: *Optimisation and Standardisation of Human Experimental Malaria Infections: Challenge by Needle and Syringe with Aseptic, Purified, Cryopreserved, Plasmodium falciparum Sporozoites (PfSPZ Challenge).* Participants were from several leading universities and institutions, mainly in Europe.

TRANSVAC

Animal model workshops

A workshop on animal models entitled *"From Bench to Trench? Necessity of animal models in pre-clinical vaccine research: required evidence for efficacy and safety"* was organised and took place in May, at CVI in Lelystad, The Netherlands. This workshop was broadly announced. A total of 30 people from the United Kingdom, The Netherland, Denmark, and Germany with broad backgrounds (regulatory, research, industry and SMEs) attended the meeting. A second workshop on animal models and statistical read-out systems took place at the Human Protection Agency (HPA) site in Porton Down in October.

Modular course in vaccine development

A modular course on concepts in vaccine development has been conceived. The course itself will be held in August 2012 and August 2013 at the University of Lausanne, Switzerland.

Vaccine Development Stakeholders Meeting and Workshops

TRANSVAC also organises a series of vaccine research and development stakeholders working groups committed to formulate and design a European roadmap aimed at securing sustainable vaccine research and development in Europe after TRANSVAC end. This road map will include tangible proposals. The foundation for this roadmap was laid during the TRANSVAC Stakeholders Meeting in Brussels in October 2010. At this meeting, EVI brought together representatives of vaccine manufacturers, biotechnology companies, academic research, regulatory authorities, product development partnerships and funding agencies to:

- Identify which activities or structures could improve the development of new vaccines and technologies in order to sustain and strengthen European leadership in the field of vaccines.
- Creating an environment in which innovation, technology development and knowledge transfer can thrive.

The first workshop was held in Brussels on in October. The main focus was on two main topics: I) How to sustain and increase support for translational vaccine research II) Training in vaccinology in Europe. The report can be found here: report workshop TRANSVAC 07-10-2011.

The recommendations made by the participants of this and future workshops will be used by the specific working groups on the two subjects: 1) Vaccine translational research and 2) Training in vaccinology. These working groups will aid in the development of a European Roadmap for Vaccine Research and Development under the coordination of the TRANSVAC consortium. This endeavour will start early 2012.
A second workshop is planned for June 2012. Please visit the website www.transvac.org for updates and information.

OPTIMALVAC

A one-day workshop was held in Heidelberg, Germany on 03 May 2010 for consortium partners. SOPs, protocols and guidance documents as well as analytical and scoring methodologies were discussed.
The workshop was divided into three parts:

- WP1: Recognition of parasite proteins by antibodies – Review of protocols, harmonisation results and statistical analysis (IFA and Western Blot)
- WP2: Definition of overall plans for testing and assessment of options (ICS and ELISpot)
- WP3 Cell-mediated immune (CMI) responses - Review of protocols, reference reagents, technical specifications (ADCI)

HARMONISATION

INYVAX

Development of the guidelines for the collection, analysis and presentation of Adverse Events Following Immunization (AEFI) in pre-licensure clinical vaccine trials in resource limited countries continued into the year with the Brighton collaboration leading the work package. A final draft document has been circulated. In addition, a template for AEFI reporting (case report form) and a template for the safety section of clinical trial protocols have been developed and are being finalised by the working group.

OPTIMALVAC

OPTIMALVAC partners exchanged standard reagents, protocols, and data analysis programmes, available on the Reference Reagents Repository (www.malariaresearch.eu), and the project website (www.optimalvac.eu). The first and second harmonisation rounds were conducted and will be pursued in the last three months of the project. The OPTIMALVAC Steering Committee chaired by Odile Leroy, met in regular teleconferences, and in a face-to-face meeting in Heidelberg in May.

The consortium also decided to extend collaboration to the external laboratories:

- National Institutes of Health (NIH), Bethesda, MD, USA
- Walter Reed Army Institute for Research (WRAIR), Silver Spring, MD, USA
- KEMRI, Kilifi, Kenya
- Infectious Disease Research Institute (IDRI), Seattle, WA, USA
- Seattle Biomedical Research Institute, Seattle, WA, USA
- ICGEB, New Delhi, India

These collaborations were extended to several African laboratories for testing standard reagents and harmonised protocols:

- Malaria Research and Training Center (MRTC), Bamako, Mali
- MRC Gambia, Banjul, The Gambia
- Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Ouagadougou, Burkina Faso
- Albert Schweitzer Hospital, Lambaréné, Gabon
- Noguchi Memorial Institute for Medical Research, Ghana

TRANSVAC

Harmonisation of immuno-assays for clinical trials

Assay harmonisation and qualification of the three main technologies: Intracellular Staining (ICS), ELISpot and antigen specific IFNγ ELISA has commenced. Standard Operating Procedures (SOPs) and protocols have been exchanged and a first stage assay harmonisation process has been completed.

An intracellular flow cytometry standard is already available. A cell-based ELISpot reference preparation is in the early stages of development

International Fora and External Communications

EVI took part in a total of twenty five international meetings, seminars, congresses etc. mainly in Europe. Flyers were distributed at selected meetings, and presentations were made at strategic meetings either on the role of PDPs or research infrastructures for vaccine development (TRANSVAC). A full detailed list of meetings attended can be found on http://www.euvaccine.eu/news-events/events/events-attended-evi. The list below reflects the meetings at which EVI was invited to give a (poster) presentation

TBVI Symposium: Future avenues for TB vaccine development, Les Diablerets, 1 February

The symposium presented the latest developments for a tuberculosis vaccine. The symposium was attended by Odile Leroy, who gave a presentation on the TRANSVAC horizontal vaccine approach.

European Conference - AIDS, Tuberculosis and Malaria Vaccines: Preparing access in Developing Countries, Paris, 15 March

The conference aimed to describe the progress being made on aspects of vaccine availability and accessibility and to identify the challenges remaining to ensure access to vaccines in developing countries. EVI was represented at the conference, held under the auspices of Friends of the Global Fund Europe, by Harry van Schooten, who gave a presentation entitled: The European vaccine strategy against poverty diseases.

Vaccines Congress, London, 4 – 5 April

The congress provided up to date insights into the discovery and development of vaccines. The Vaccines Congress also covered new and novel technologies for vaccines design, development and delivery, implementation of successful clinical trials, as well as current developments in vaccine process development and production. Attendees at the event benefited from strategies to lower cost and time to first dose, increase yield and optimise pipeline in Vaccines Discovery and Development. Odile Leroy spoke at the congress on: The European Vaccine Initiative - Translational Research and Lessons Learned from Malaria Vaccine Development.

Immunopotentiators in Modern Vaccines, Porto, 6 – 8 April

Immunopotentiators in Modern Vaccines (IMV) 2011 once again offered an international forum to review the current state of research and developments/applications of immunopotentiators/adjuvants for modern vaccines and associated vaccine programmes/strategies. The conference was of interest to researchers involved in determining the mechanisms of adjuvant function and responses and optimising these responses, manufacturers of biologicals, those involved in the manufacture licensing of injectable biologicals, and those interested in the control of infectious and non-infectious diseases. EVI held a workshop on the EC-funded project PHARVAT in connection with this event to discuss the proposed adjuvant testing method and amend it based on stakeholder recommendations. The event was attended by Regitze Thøgersen and Sophie Houard. Regitze gave a poster presentation on the main objectives of PHARVAT.

7th Annual BioMalPar Conference: Biology and Pathology of the Malaria Parasite, Heidelberg, 16 – 18 May

The conference was sponsored by the European Network of Excellence, EVIMalaR. The purpose of the BioMalPar annual conference was to bring together malaria researchers from Europe and overseas (including Africa, America, Asia and Australia) in order to present and share recent groundbreaking findings on fundamental malaria research. New insights were also featured through the use of poster sessions. This meeting also provided an enriched environment for researchers at all stages of their careers to interact with international leaders in the field. The meeting offered an excellent opportunity for sharing ideas and for potential development of new worldwide collaborations.

The conference was attended by Odile Leroy, Sophie Houard, Mark Geels, Regitze Thøgersen and Nathalie Imbault. The conference included a European Malaria Vaccine Development Association (EMVDA) session on 18 May. Members of the EMVDA consortium and of its External Scientific Advisory Committee also attended the conference. Mark Geels presented a poster on the EVI coordinated TRANSVAC research infrastructure titled: 'TRANSVAC: European Network of Vaccine Research and Development'

4th Congress of the Federation of European Microbiological Societies (FEMS), Geneva, 26 – 30 June

The congress offered professionals the latest information on microbiology, an in-depth understanding of the interdependence between key fields, and a chance to discuss solutions to future challenges.

Odile Leroy gave an introductory statement at the round table discussion on 27 June on the translation of basic research in microbiology into its clinical application and the ways how the European community funding structures can support such activities.

6th Conference on Global Health and Vaccination Research "Contributions to Global Health Research, Capacity Building and Governance", Oslo, 12 – 13 September

The conference gave national and international researchers, health professionals and decision-makers a mutual meeting point to discuss key issues and suggest future policies. It was also the Norwegian Medical Association's 125th Anniversary conference. The aim was to enhance our understanding of how Norwegian key partners, in cooperation with the global health community, can contribute to bridge the research gap by strengthening research, capacity building and governance.

The conference was attended by Odile Leroy and Harry van Schooten who gave a presentation entitled: Developing Vaccines for Diseases of Poverty: How far are we?

7th European Congress on Tropical Medicine and International Health, Barcelona, 3 – 6 October

The congress included traditional aspects of the Tropical Medicine seen through health research and patient care developed by European institutions and their partners. However, this time the congress placed more emphasis on new concepts and practices in global health under the motto "Global Change, Migration and Health". We believe that the surveillance and prevention of diseases in an era of migration and global change are issues on which the voice of the European federation must be heard, and this was a unique opportunity for open debate, discussion and presentation of practical examples from which central global international health institutions could benefit.

Harry van Schooten gave a presentation entitled: Developing Vaccines for Diseases of Poverty: How far are we?

World Vaccine Congress, Lyon, 10 – 13 October

The World Vaccine Congress Lyon was a multi-faceted event. The four day conference covered case studies by industry professionals, speed networking, interactive panel discussions, roundtable brainstorms and live debates.

Odile Leroy gave a presentation entitled: The role of the EVI today. Mark Geels gave a presentation entitled: How to strengthen the vaccine research infrastructure in Europe? The role of TRANSVAC. (http://youtu.be/Nl8Kab9aIjI)

Vaccines Europe 2011, Brussels, 30 November – 1 December

The conference focused on vital topics including emerging vaccine markets, vaccine characterisation, quality control, scale-up and manufacturing. Vaccines Europe is a hugely successful event attracting some of the leading international experts, academics and service providers in the industry. This conference also provided talks on the latest cutting edge research and technologies in new vaccine targets.

Mark Geels gave a presentation entitled: From technical development of Malaria Vaccines to other diseases of poverty vaccines. Sophie Houard also participated.

GOVERNANCE & FUND RAISING

GOVERNANCE

EVI was formally established as a European Economic Interest Grouping (EEIG) by a set of statutes signed in August 2009 between the founding Universities of Stockholm and Heidelberg, and in March 2011 four new institutions were registered in the European Economic Interest Grouping, which is the legal identity of EVI:

Biomedical Primate Research Centre (BPRC) in The Netherlands

Jenner Vaccine Foundation, University of Oxford, UK

National Institute for Public Health and the Environment (RIVM), The Netherlands, and

Royal College of Surgeons in Ireland (RCSI), Republic of Ireland.

EVI ultimate decision-making body is the EVI Board. This is overseen by a Board of Stakeholders, which has powers to make recommendations to the EVI Board on governance and good practice.

The EVI Board receives advice and recommendations for approval, in areas such as scientific strategy and which grant applications to fund, from an independent Scientific Advisory Committee.

Implementation of EVI Board decisions is the responsibility of the Secretariat. EVI is hosted by the UniversitätsKlinikum Heidelberg, which serves as EVI headquarters.
The EVI EEIG has signed two memoranda of understanding, one with the Brighton Collaboration Foundation to further strengthen the collaboration established during INYVAX, one with the Malaria Vaccine Development Programme to synergise the activities of the two initiatives for the development of malaria vaccine.

FUND RAISING

In June EVI successfully submitted a request for funding to the Irish Aids. The five year grant agreement between Irish Aids and EVI was executed on 16th November. The total budget is €5 million.

In September, EVI successfully submitted an application to the BMBF call: "Development of Products for the Prevention, Diagnosis and Treatment of Neglected and Poverty Related Diseases"
The BMBF has agreed to fund the development of pregnancy associated malaria vaccine with a budget of € 4,432,025 matched with cofounding form EVI, and the partners of the application.
In October, EVI applied to the EC FP7 Research and Innovation Health 2012 call with 10 applications for SME-led consortia. The whole EVI team was mobilised to ensure timely delivery of all proposals in close collaboration with our partners. EVI was especially delighted to submit proposals with first-time partners such as SME's Sanaria & Ancora (US) and Confarma (FR), CNRS Centre de Recherche de Biochimie Macromoléculaire (F), University of Heidelberg (Department of Parasitology and Heidelberg school of Medicine) and Max Planck institutes in Berlin and Potsdam. EVI's main goal was to show to EC that amongst our partners still a significant amount of important and viable malaria vaccine concepts are present which merit consideration and further development. Especially since it is unclear how the current unknown post-RTS,S malaria vaccine landscape will be filled. Of the 10 applications three were requested to submit a full proposal in the first week of February 2012.
EVI applied in December 2011 with the University of Oslo and the International Centre for Genetic Engineering and Biotechnology (ICGEB) New Delhi for the third New INDIGO call for research projects in the field of Biotechnology applied to Human Health. The proposal brings together the innovative new vaccine technology Vaccibodies which was developed at the University of Oslo and promising Malaria targets identified by

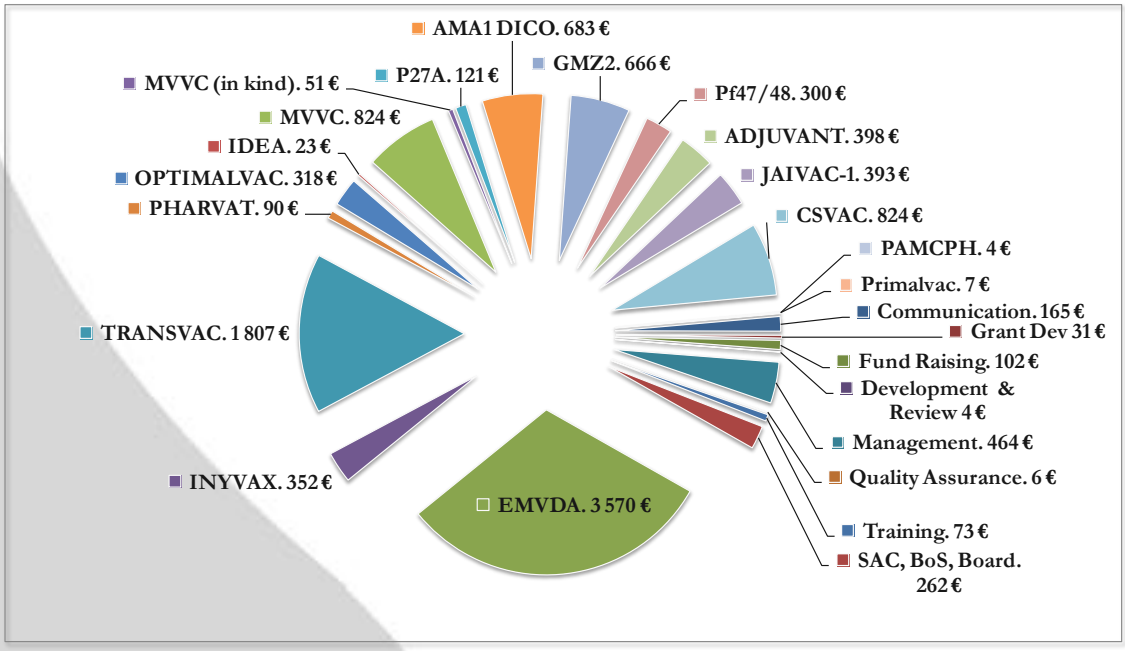
ICGEB. The proposal includes request for research costs, personnel costs, mobility and three workshops.

FINANCIAL UPDATE 2011

The year 2011 was an uplifting year for EVI. From a financial point of view we have seen acknowledgement of our work resulting in a new donor and a renew grant from another. We have seen positive developments in vaccine development, whereby projects have progressed from GMP to clinical trials, and in our EC projects significant deliverables and milestones have been efficiently met, which is evident in the financial figures. EVI staff has, in the current reporting period, once again shown diligence and a high level of accomplishment in all areas of EVI activities. 2011 has been yet another economically difficult year for our donors, in these times of continued economic stagnation. However, we are indebted for their strong support, and we would like to extend our heartfelt thanks to Irish Aid, DGIS, BMBF, EDCTP, and the EC for their invaluable encouragement.

Figure 2 below shows the cost activity over the current reporting period, where expenditure in the broad portfolio of EVI, EDCTP and EC projects, has technically produced a high level of outcome in comparison with the level of funding. The financial conclusion of the current reporting period is that EVI performance is continuously improving and that funds are properly utilised to accelerate the development of vaccine against diseases of poverty. In this respect, it is noteworthy that management costs account for only 4.02% of total expenditure.

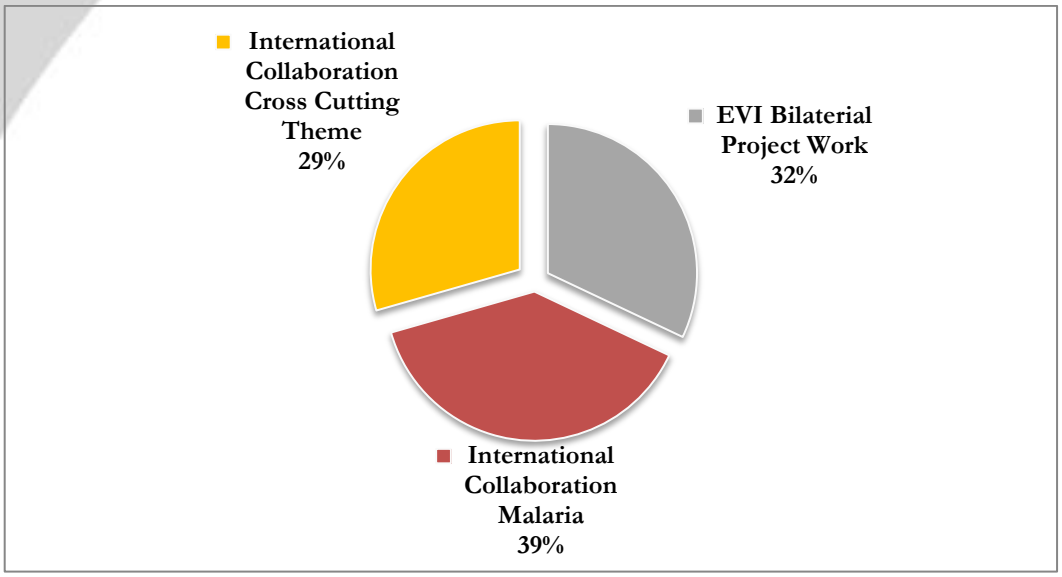
Figure 2 - Total EVI Activity 2011 (€'000)



INTERNATIONAL COLLABORATIONS

EVI is more than anything an international organisation collaborating on malaria and other cross cutting vaccine themes through coordination and networking on a global level. In 2011 68% of EVI activities was direct international collaboration with partners and stakeholders from Europe, Africa, Asia and North America. 32% was bilateral work, which by its nature, also counts as international collaboration. See figure 3.

Figure 3 – International Collaborations



EVI PROJECT ACTIVITIES

Over the past 12 Months the EVI vaccine portfolio has seen immense activity. cGMP manufacturing is on-going, and clinical trials are progressing surely and steadily. During the next 12 months a high level of investment is predictable, as the projects progress forward.

Figure 4 - EVI Portfolio Investment (€'000)

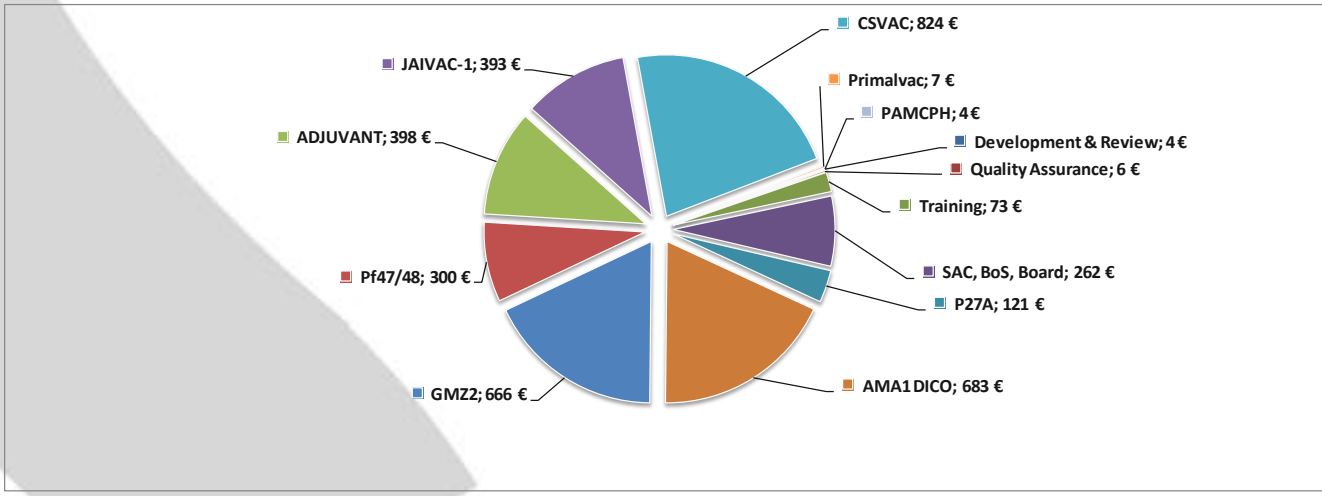
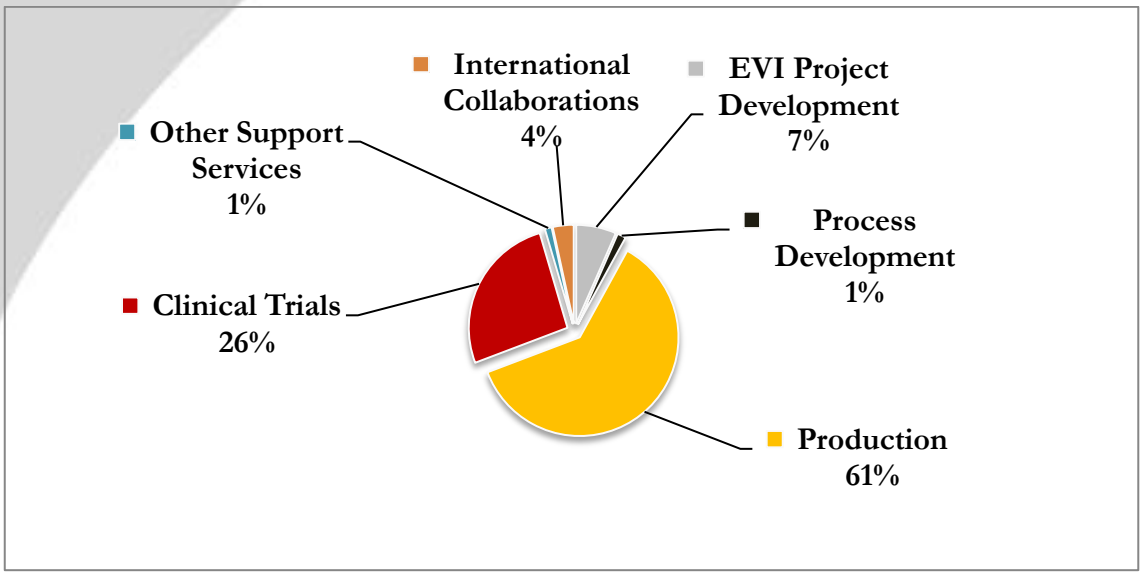


Figure 5 depicts investment over the past 12 months dominated by cGMP and clinical trials. Investment over the next 12 months will continue to be dominated by cGMP and clinical trials, including investments in process development, especially for the Pregnancy Associated Malaria projects.

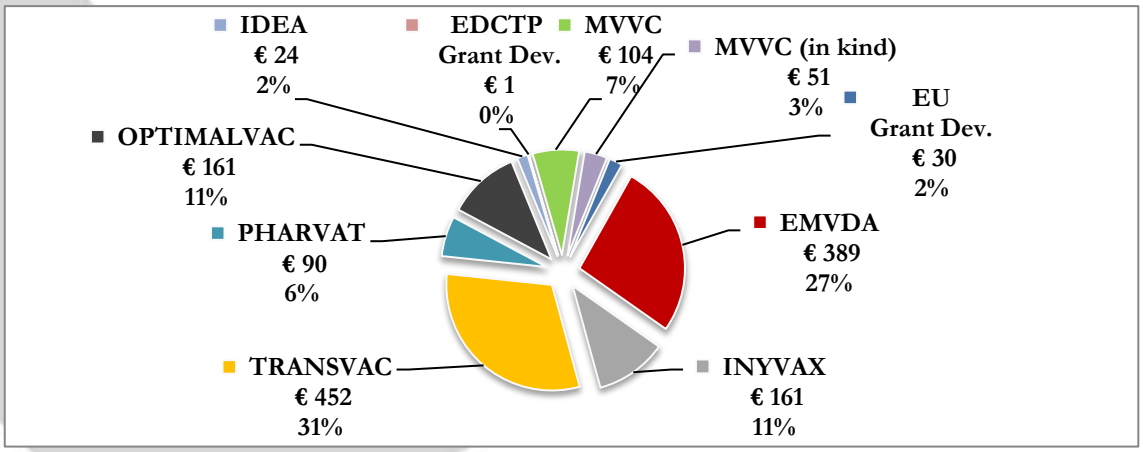
Figure 5 - Portfolio investment type in %



EVI EC & EDCTP Activity

Besides the EVI portfolio of specific investment in various vaccine candidate projects, EVI is involved in several EC and EDCTP funded projects. Figure 6 shows expenditure less partner transfers, i.e. solely attributed to EVI. Not surprisingly, the largest expenditure is attributed to the EC project TRANSVAC (budget €9.9 Million). EMVDA has also seen increased activity. INYVAX and OPTIMALVAC continue their steady progression towards conclusion at the end of 2012 as planned, and MVVC is ongoing according to plan.

Figure 6 - EC and EDCTP (MVVC) Activity (€'000 and in %)

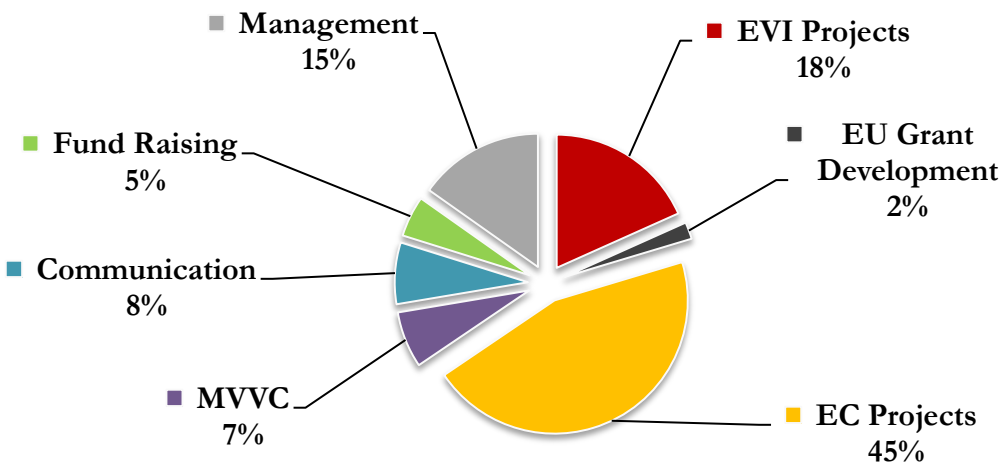


STAFF TIME (HOURS) IN THE CURRENT REPORTING PERIOD

In 2011 EVI managed to pick up speed on the EC projects as reflected in the figure below. Although staff spent 15% of their time on management, overall management expenditure only accounted for 4.02% of total global expenditure. The goal is not to exceed the current staff hours on management in 2012.

At the start of EVI's activity, almost all staff were based at offices around Europe, making EVI a de-facto virtual organisation. By the end of 2010 most staff where based at EVI Headquarters in Heidelberg, Germany. At the end of 2011 only four members of staff are placed outside of Germany, two of which are at the registered office in Denmark. The strategy of EVI is to strengthen the executive office and continue to reduce expenditure on consultants, which was implemented in 2011.

Figure 7 - Staff time - Hours – in %



FINAL REMARKS

EVI would like to thank all of our donors, stakeholders, subcontractors and partners in vaccine development. We would, from a financial point of view, like to extend our appreciation to the BDO offices in Germany, France, Belgium, Denmark and United Kingdom for well organised payroll management and tax advice. EVI sends especial thanks to LETT law firm in Copenhagen for dealing efficiently and professionally with our rights in Denmark, and FALK & co in Heidelberg for their role as financial auditor of EVI.

In the following section a supporting detailed analysis of the figures from the Profit and Loss and Balance sheet is presented.

Principal accounting policies

(a) Basis of accounting

The basis of accounting is in accordance with German GAAP "General Accepted Accounting Principles". Other accounting policies are described in the EVI handbook together with relevant policies known and applied by EVI staff. EVI accounting method is accrual based, except for projects governed by external guidelines.

(b) Transfer from EMVI to EVI

In 2011 a settlement was reached between EVI and SSI, which concluded the transfer of funds. The amount, which is shown under Balance overview by donor and EC/EDCTP funds under Received 2011, is allocated to relevant donors.

(c) Realised Income policy

Grants/donations received by EVI are posted on the balance sheet. Grant related expenditures are posted on the Profit and Loss (PNL), and as such figure as income for EVI. Only income generated from sales or other economic activity is directly recognised as income on the PNL.

(d) Payables

All amounts payable by EVI are charged to the PNL in the cost relevant year.

(e) Investment income and interest receivable

Interest received on EVI funds is included in the PNL in the year for which it is receivable. It is posted on the EVI administrative cost centre, and can be utilised as core support.

(f) Funds accounting

Funds held by EVI are either:

• Core support funds – these are funds set aside for eligible project relevant expenditures.

• Restricted funds – these are funds related to specific projects including EC projects.

(g) Foreign currencies

Transactions in foreign currencies are translated into Euro at rates prevailing on the date of the transaction using xe.com, with the one exception of Danish Kroner which is politically fixed at a rate of 7.45. EVI has for the year 2011 made use of the following currencies: EUR, DKK, INR, USD and XOF. In 2012 EVI will introduce the European Central Bank (ECB) rate for EC projects as recommended by the EC auditors.

(h) Auditor

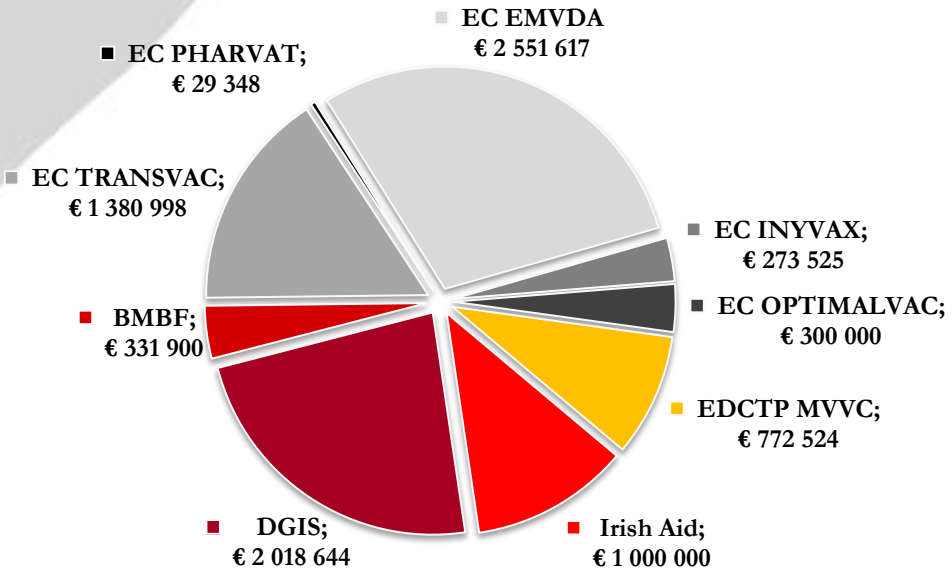
EVI is audited by FALK & Co, who forms part of the global alliance of independent firms called PRAXITY.

The auditor issues the audit report, which is made available in full to the EEIG Board members and Board of Stakeholders, including all donors and the EC. The audit report contains analysis of EVI and relevant recommendations by the auditor.

In the current annual report the conclusion – the auditor's opinion - together with the audited profit and loss and balance sheet is shown and made public. The opinion is shown in German and an English translation prepared by the auditor.

Grants received

Figure 8 – Grant Received in €



Interest earned

Interest Danish Account	€	243
Interest German Account	€	14,163
Interest SSI	€	267,221
Total	€	281,627

EVI extends its thanks and appreciation to all its Donors and Grant providers

Staff

List of staff (as at 31 December 2011)

	First Name	Last Name	Title/Function in EVI	Location
1	Odile	Leroy	Executive Director	Germany
2	Mark	Geels	Project Manager	Germany
3	Nathalie	Imbault	Quality Assurance, External Relations & Communication, Director	Germany
4	Roland	Kleine	Office Clerk	Germany
5	Thorsten	Kohaut	Accounting Assistant	Germany
6	Sandra	Theilig	Personal Assistant	Germany
7	Joel	Thoegersen	Trainee Project Manager	Germany
8	Nicola	Viebig	Project Manager	Germany
9	Nicolas	Havelange	Production, Director*	Belgium
10	Sophie	Houard	Vaccine Development Manager	Belgium
11	Egeruan Babatunde	Imoukhuede	Clinical & Regulatory Affairs, Director	UK
12	Sten	Larsen	Finance & Human Resource, Director	Denmark
13	Jill	Iversen	Web Master*	Denmark
14	Regitze Louise	Thoegersen	Program Manager	Denmark
15	Harry	Van Schooten	Public Health & Business Development Advisor*	The Netherlands
16	Pierre	Druilhe	Scientist (OPTIMALVAC WP2)*	France

*Consultant

Men	9
Women	7
Total Staff of EVI 31 December 2011	**16 (13 FTE)**

Direct & indirect project expenditures

Grants, contracts, & direct assistance

Contracts - programme-related	€	3,311,020
Grants to other organisations	€	150,000
Benefits paid to or for MVVC consortium members	€	720,840
Benefits paid to or for EC consortium members	€	4,881,866
Total Payables	**€**	**9,063,726**

Salaries & wage expenses:

Salaries & wages international staff	€	262,371
Salaries & wages German staff	€	340,223
Employee benefits & social security - not pension	€	299
Payroll taxes, etc.	€	297,114
In house consultancies.	€	235,394
Statutory social security expenses	€	179,864
Contributions to health and safety agency	€	8,611
Holiday pay accrued	€	90,083
Total salary cost	**€**	**1,413,960**

Contract service expenses

Fundraising fees	€	358
Accounting fees	€	67,832
Legal fees	€	84,369
Professional fees - other	€	6,657

Facility & equipment maintenance expenses:

Outside computer services	€	91
Software Licenses	€	33,396
Mailing services	€	17
Repairs and maintenance	€	959
Publishing cost incl. copy and printing	€	40,225
Publishing cost incl. copy and printing – sub contacting	€	550
Books, subscriptions, references	€	741
In-house publications	€	2,975

Equipment, hardware & software

Minor hardware purchases	€	2,511

Minor software purchases	€	3,272
Minor furn., fix., equip, vehicle parts	€	449
Depreciation & amortisation	€	10,291

Travel & meetings expenses:

Travel (flights)	€	85,444
Travel (train, ferry, taxi, other)	€	44,678
Travel (refund for own use of travel means)	€	5,302
Hotel and other accommodation costs	€	62,762
EC hotel and other accommodation costs	€	2,238
Conferences, conventions, meetings	€	14,693
EC conferences, conventions, meetings	€	54,274
EDCTP conferences, conventions, meetings	€	1,857
Travel allowances for employees	€	21,858
EDCTP travel allowances for employees	€	366
Restaurant, catering and other travel provisions	€	2,311
EC restaurant, catering and other travel provisions	€	2,424
External staff training costs	€	874
External staff teambuilding costs	€	11,516
Total travel cost	**€**	**310,596**

Other direct expenses:

Recruitment costs	€	100
Insurances	€	6,741
Internal staff training costs	€	9,541
Internal staff teambuilding costs	€	17,803

Indirect business expenses:

Utilities (heat, water, electricity costs)	€	110
Telephone & telecommunications	€	16,438
Broadband & other internet connections	€	146
Postage & shipping	€	10,698
Office supplies	€	38,019
Fees & charges	€	20,536
Hosting agreement costs	€	130,000
Organisational (corp.) expenses	€	199,848

Board, BoS & SAC expenses:

Board meetings	€	579
Board travel cost	€	5,143

BoS meetings	€	138
BoS travel cost	€	9,088
SAC meetings	€	6,974
SAC travel cost	€	12,785

EC ESAC, SAC, SC expenses:

ESAC travel cost	€	5,368
SAC meetings	€	1,800
SAC travel cost	€	2,839

Total expenses	**€**	**11,537,671**

Major payables

EVI project payments	Project relevance	Amount
BPRC	ADJUVANT	€ 150,000
IDRI	ADJUVANT	€ 114,303
Serum Institute of India	ADJUVANT	€ 37,150
Confarma	AMA1 DiCo	€ 12,396
Fraunhofer IME	AMA1 DiCo	€ 685,373
Nova Labs	AMA1 DiCo	€ 13,120
Output Pharma	AMA1 DiCo	€ 9,182
Rita Walt Consulting	AMA1 DiCo	€ 34,916
RCSI	CSVAC	€ 201,000
UOXF	CSVAC	€ 589,700
EMBL	EMVDA sub.	€ 258,819
Statens Serum Institut	GMZ2	€ 665,249
Diagnosearch Life Science	JAIVAC	€ 137,250
ICGEB	JAIVAC	€ 172,163
Almac Sciences Ltd	P27A	€ 60,400
Radboud University	Pf48/45	€ 300,000
Betty Dodet Bioscience	TRANSVAC sub.	€ 20,000

MVVC project payments	Project relevance	Amount
CNRFP	MVVC	€ 149,277
KEMRI	MVVC	€ 130,230
MRC Gambia	MVVC	€ 69,451
Okairos SRL	MVVC	€ 2,380
UCAD	MVVC	€ 135,517
UOXF	MVVC	€ 210,467
VSCR	MVVC	€ 23,517

EC project payments	Project relevance	Amount
AMANET	EMVDA	€ 18,503
BPRC	EMVDA	€ 54,894
CHUV	EMVDA	€ 1,631,773
EKUT	EMVDA	€ 729
ETNA	EMVDA	€ 65,848

EVI project payments	Project relevance	Amount
MRC	EMVDA	€ 1,002
RUNMC	EMVDA	€ 109,184
SSI	EMVDA	€ 314,805
STI	EMVDA	€ 847
SU	EMVDA	€ 7,625
UEDIN	EMVDA	€ 13,063
UHEI	EMVDA	€ 716,984
UOXF	EMVDA	€ 245,844
BPRC	INYVAX	€ 26,838
Brighton Collaboration	INYVAX	€ 39,083
FMER	INYVAX	€ 49,204
TBVI	INYVAX	€ 24,427
University of Geneva	INYVAX	€ 7,455
WHO (GADI)	INYVAX	€ 43,129
BPRC	OPTIMALVAC	€ 16,810
CRESIB	OPTIMALVAC	€ 15,220
Institut Pasteur	OPTIMALVAC	€ -53,985
RUNMC	OPTIMALVAC	€ 39,573
University of Edinburgh	OPTIMALVAC	€ 71,345
UOXF	OPTIMALVAC	€ 12,418
WHO	OPTIMALVAC	€ 54,793
BPRC	TRANSVAC	€ 37,001
HPA-CEPR	TRANSVAC	€ 132,893
HZI	TRANSVAC	€ 30,425
IDL	TRANSVAC	€ 86,616
LIONEX	TRANSVAC	€ 322,691
LSHTM	TRANSVAC	€ 57,133
MPIIB	TRANSVAC	€ 504,385
UOXF	TRANSVAC	€ 150,761
TBVI	TRANSVAC	€ 23,540
VPM	TRANSVAC	€ 9,010

Expenditures by project

PROJECT CODE	Amount spent (incl. partner pay)		In percentage
P27A	€	120,951	1.0%
AMA1	€	683,179	5.9%
GMZ2	€	666,465	5.8%
Pf45/48	€	300,000	2.6%
ADJUVANT	€	397,690	3.4%
JAIVAC-1	€	393,071	3.4%
CSVAC	€	823,708	7.1%
PriMalVac	€	6,791	0.1%
PAMCPH	€	3,881	0.0%

Quality Assurance	€	6,389	0.1%
Development & Review	€	4,349	0.0%
Training internal/external	€	72,814	0.6%
Reporting/working with SAC, BoS & Board	€	261,580	2.3%

EC Grant development	€	30,311	0.3%
EMVDA	€	3,569,889	30.9%
INYVAX	€	351,571	3.0%
TRANSVAC	€	1,806,727	15.7%
PHARVAT	€	90,371	0.8%
OPTIMALVAC	€	317,568	2.8%
IDEA	€	23,473	0.2%

EDCTP Grant Dev.	€	260	0.0%
EDCTP VV (financed)	€	824,918	7.1%
EDCTP VV (in kind)	€	51,007	0.4%

Communication	€	165,127	1.4%
Fund Raising	€	101,527	0.9%

Management	€	464,056	4.0%
TOTAL	**€**	**11,537,671**	**100%**

Balance overview of donor and EC/EDCTP funds

Donator/Grant	Type	Balance 31/12 2010	Received 2011	Cost 2011	Balance 31/12 2011
Irish Aid - IE	Core	**2,385,071**	1,537,406	2,750,126	**1,172,351**
Board Funds - EVI	Core	**1,280,780**	1,986,459	4,207	**3,263,032**
BMBF - DE	Restricted	**-**	331,900	11,419	**320,481**
DGIS - NL	Restricted	**461,417**	2,553,993	2,182,387	**833,023**
TRANSVAC - EC	Restricted	**432,022**	1,380,998	1,806,727	**6,293**
PHARVAT - EC	Restricted	**30,292**	29,348	90,370	**-30,732**
IDEA - EC	Restricted	**54,525**	-	23,473	**31,052**
INYVAX - EC	Restricted	**50,586**	275,379	351,570	**-25,605**
OPTIMALVAC - EC	Restricted	**88,827**	384,785	400,537	**73,075**
EMVDA - EC	Restricted	**1,082,095**	2,816,412	3,582,318	**316,189**
MVVC - EDCTP	Restricted	**74,517**	772,524	824,918	**22,123**
ADMIN EVI	Core	**433,890**	1,044,825	370,259	**1,108,456**
Total core		**4,099,741**	**4,568,690**	**3,124,592**	**5,543,839**
Total restricted		**2,274,281**	**8,545,339**	**9,273,719**	**1,545,901**
Total EVI funds		**6,374,022**	**13,114,029**	**12,398,311**	**7,089,740**

Cash management (bank accounts) as at 31st December 2011

Cash in bank (EUR)	€ 4,275,423.83
Cash in Danish Bank (DKK)	€ 34,497.90
Savings accounts (EUR)	€ 5,000,000.00

Hosting costs

EVI is hosted by the Heidelberg University with the following costs:

Hosting costs – Legal support € 65,000
Other charges € 790.58

Total 2011 service charges € 65,790.58 (2010 = € 66,589)

Remuneration of governing bodies

Travel and subsistence costs are refunded to Board, BoS and SAC members in connection with meetings and conferences including a honorarium to SAC members.

We formally sign and approve the EVI Annual Financial Report for the year 2011 ending 31st December 2011 in accordance with EVI-EEIG Board decision.

The governing accounting principles and the overall presentation of the Annual Financial Report are deemed to give a true and fair illustration of EVI activities.

Date : 21-03-2011

Odile Leroy, EVI Executive Director

Date : 21-03-2011

Sten Larsen, EVI Finance Director

Date : 21-03-2011

Marita-Troye Blomberg, Chair of EVI-EEIG Board

Financial statements as audited for the year ending 31st December 2011

PNL and Balance sheet to be updated ASAP by STL after release by Auditor Falk & Co

Income Statement	€ 2011	€ 2010
1. Other operating income from donors	11,256,044.20	12,887,073.02
2. Miscellaneous operating income	0.00	617.00
3. Subtotal I	**11,256,044.20**	**12,887,690.02**
4. Personal wages		
a. Wages and Salaries	-1,225,185.74	-964,200.10
b. Social security costs	-188,774.25	-221,049.56
c. Thereof for pensions: € 0.00	0.00	0.00
	-1,413,959.99	**-1,185,249.66**
5. Depreciation on Tangible fixed Assets	-10,291.12	-3,166.37
6. Other operating Expenses	-10,113,420.00	-11,722,714.28
7. Subtotal II	**-281,626.91**	**-23,440.29**
8. Other Interest and similar income	281,626.91	23,440.29
9. Net Result	**0.00**	**0.00**

Balance Sheet		€ 2011		€ 2010
Assets				
A. Fixed Assets				
Tangible Assets				
Other Equipment, office and plant equipment		**27,706.96**		**9,499.05**
B. Current Assets				
I. Other Assets				
Other Assets	10,948.65		12,280.33	
II. Cash in hand, Cash in Banks	9,309,921.73	**9,320,870.38**	7,295,293.97	**7,307,574.30**
		9,348,577.34		**7,317,073.35**

Liabilities and Shareholders' Equity		€ 2011		€ 2010
A. **Accruals**				
Other Accruals		**1,885,216.57**		**885,766.00**
B. **Liabilities**				
1. Liabilities in relation to grants received				
a. National governments grants liabilities	5,543,839.12		4,099,740.72	
b. European Union and other restricted grant liabilities	1,545,900.20		2,274,281.76	
Thereof with a remaining term up to one year	7,089,739.32		6,374,022.48	
2. Creditors (Trade payables)	338,448.80		0.00	
3. Other Liabilities	35,172.65		57,284.87	
thereof from taxes	17,549.14		14,637.71	
thereof from social security	157.75		24,054.28	
thereof with a remaining term of up to one year	35,172.65	**7,463,360.77**	57,284.87	**6,431,307.35**
		9,348,577.34		**7,317,073.35**

Acknowledgements

Grateful thanks are extended to the following people, who have contributed significantly to the success of EVI: Especially all the participants in the clinical trials funded by EVI.

Our Board Members and Donors:

Andreas	Holtel	Belgium
Brian	Greenwood	United Kingdom
Charles	de Taisne	France
Charles	Mgone	Tanzania
Christos	Profilis	Greece
Claire	Boog	The Netherlands
Claus	Bartram	Germany
Clemens	Kocken	The Netherlands
Diarmuid	McClean	Republic of Ireland
Diarmuid	O'Donovan	Republic of Ireland
Marita	Troye-Blomberg	Sweden
Marja	Esveld	The Netherlands
Sodiomon	Sirima	Burkina Faso
Suresh	Jadhav	India
Terry	McWade	Republic of Ireland

Our Scientific Advisors:

Aissatou	Toure	Senegal
Alister	Craig	UK
Juhani	Eskola	Finland
Mahamadou Aly	Thera	Mali
Roland	Dobbelaer	Belgium
Samuel	McConkey	Republic of Ireland

Our Partners

Academisch Medisch Centrum bij de Universiteit van Amsterdam	NL
Academisch Ziekenhuis Leiden – Leids Universitair Medisch Centrum	NL
African Malaria Network Trust	TZ
Agence Nationale de Recherches Sur Le Sida et les Hépatites Virales	FR
Albert Schweitzer Hospital	GA
ALMAC Sciences	UK
Barcelona Center for International Health Research	ES
Bharat Biotech	IN
Biomedical Primate Research Centre	NL
Brighton Collaboration Foundation	CH

Centers for Disease Control and Prevention	USA
Central Veterinary Institute	NL
Centre Hospitalier Universitaire Vaudois	CH
Centre National de Recherche et de Formation sur le Paludisme	BF
CiToxLAB	FR
Confarma	FR
DiagnoSearch Life Sciences Pvt. Ltd.	IN
Eberhard-Karls Universität Tübingen	DE
Ecole Polytechnique Federale de Lausanne	CH
Etna Biotech	IT
Eurovacc Foundation	NL
Fondation international de l'Hopital de Dr. Albert Schweitzer de Lambarene	GB
Fondation Mérieux	FR
Fraunhofer IME	DE
Gregory Fryer Associates Ltd	UK
Health Protection Agency – CPER	UK
Health Protection Agency/ National Institute for Biological Standards and Control	UK
Helmholtz Zentrum für Infektionsforschung GmbH	DE
Henogen (now novasep)	BE
Ifakara Health Institute	TZ
ImmunoVacc Consulting	BE
Infectious Diseases Research Institute	USA
Institut National de la Sante et de la Recherche Medicale	FR
Institut Pasteur	FR
International Centre for Genetic Engineering and Biotechnology	IN
Intox Pvt. Ltd	IN
Istituto Nazionale Malattie Infettive L.Spallanzani – IRCCS	IT
Jenner Instiute	UK
Kenya Medical Research Institute	KE
LIONEX GmbH	DE
London School of Hygiene and Tropical Medicine	UK
Lotus Labs. Pvt. Ltd.	IN
Ludwig-Maximilians-Universitaet München	DE
Makerere University	UG

Malaria Consortium LBG	UK
Malaria Vaccine Development Program	IN
Max Planck Institute for Infection Biology	DE
Medical Research Council, Gambia	GM
Medical Research Council on behalf of its MRC/UVRI Uganda Research Unit on AIDS	UK
National Institute for Medical Research	UK
National Institute for Medical Research – Mbeya Medical Research Program	TZ
Navrongo Health Reseach Centre	GH
NNE Pharmaplan GmbH	DE
Nova Laboratories Ltd	UK
Okairòs srl	IT
Output Pharma	DE
PATH Malaria Vaccine Initiative	USA
Pevion Biotech	CH
Radboud University Nijmegen	NL
Royal College of Surgeons in Ireland	IE
Ruprecht-Karls-Universität Heidelberg	DE
Statens Serum Institut	DK
Serum Institute of India	IN
Stockholm University	SE
Swiss Tropical Institute	CH
The Chancellor of Masters and Scholars of the University of Oxford	UK
TuBerculosis Vaccine Initiative	NL
Université Cheikh Anta Diop	SN
Université de Genève	CH
University of Edinburgh	UK
University of Ibadan	NI
University of Lausanne	CH
University of Lausanne (WHO reference centre)	CH
University of Oxford	UK
University of Stockholm	SE
Vakzine Projekt Management GmbH	DE
Vienna School of Clinical Research	AT
World Health Organization	CH

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