EUROPEAN VACCINE INITIATIVE

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For Donors

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European Vaccine Initiative
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List of Abbreviations

7G8	Brazilian Pf line
Ad	Adenovirus
ADCI	Antibody-Dependent Cellular Inhibition
ADVAC	Advanced Training in Vaccinology
AEFI	Adverse Effects Following Immunisation
AERAS	A global non-profit biotechnology organisation with a mission to develop new tuberculosis vaccines that are affordable and accessible to all who need them.
Ag	Antigen
AIDS	Acquired Immune Deficiency Syndrome
AMA1	Apical Membrane Antigen 1
ANSM	Agence nationale de sécurité du médicament et des produits de santé
ASH	Albert Schweitzer Hospital
ASTMH	American Society of Tropical Medicine and Hygiene
AT	Austria
BCG	Bacillus Calmette-Guérin
BCTU	Bagamoyo Clinical Trial Unit
BE	Belgium
BN	Benin
BELLEROPHON	A project combining cellular and humoral immune responses as a vaccine strategy against *Staphylococcus aureus* pathogen
BF	Burkina Faso
BMBF	German Federal Ministry of Education and Research
BMGF	Bill and Melinda Gates Foundation
BoS	Board of Stakeholders
B. pertussis	*Bordetella pertussis*
BPRC	Biomedical Primate Research Centre
CBF	Cell Banking Facility
CCEV	Commission Cantonale d'Ethique Vaudois
CD	Cluster of Differentiation
CDC	Centres for Disease Control
CERPAGE	Centre d'Étude et de Recherche sur le Paludisme Associé à la Grossesse et l'Enfance
cGMP	Current Good Manufacturing Practice
CH	Switzerland
ChAd	Chimpanzee Adenovirus
ChAd63	Chimpanzee Adenovirus 63
CHMI	Controlled Human Malaria Infection
CHUV	Centre Hosptalier Universitaire Vaudois
CIC	Clinical Investigational Centre
CD	Cluster of Differentiation
CMI	Cell-Mediated Immunity
CMO	Contract Manufacturing Organisation

CMP	Centre for Medical Parasitology
CNRFP	Centre National de Recherche et de Formation sur le Paludisme
CoA	Certificate of Analysis
COSSEC	Comité d'orientation stratégique et de suivi des essais clinique
CPP	Comité de Protection des Personnes Ile de France III
CRO	Contract Research Organisation
CS	Circumsporozoite
CSA	Chondroitin Sulphate A
CSP	Circumsporozoite Protein
CSVAC	A Circumsporozoite Protein Vaccine against malaria using the adenovirus Ch63 vector
CT	Clinical Trial
CTA	Clinical Trial Application
CTP	Clinical Trial Protocol
CVI	Central Veterinary Institute
DBL	Duffy-Binding-Like
DC	Developing Countries
DCVMN	Developing Countries Vaccine Manufacturer Network
DE	Germany
DG	Directorate General
DGIS	Directorate General for International Cooperation at the Ministry of Foreign Affairs
DiCo	Diversity Covering
DK	Denmark
DNA	Deoxyribonucleic acid
DP	Drug Product
DoP	Disease of Poverty
DS	Drug Substance
DSMB	Data Safety Monitoring Board
EATRIS	European Advanced Translational Research Infrastructure in Medicine
EBA	Erythrocyte-Binding Antigen
E. coli	*Escherichia coli*
EC	European Commission
ECBS	Expert Committee on Biological Standardisation
EDCTP	European and Developing Countries' Clinical Trials Partnership
EDUFLUVAC	Educate Influenza Vaccine
EEIG	European Economic Interest Grouping
EKUT	Eberhard Karls Universität Tübingen
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immuno Spot Assay
EMA	European Medicines Agency
EMVDA	European Malaria Vaccine Development Association
EMVI	European Malaria Vaccine Initiative
EPI	Expanded Programme on Immunization
ESAC	External Scientific Advisory Committee

ESI-MS	Electrospray Ionisation Mass Spectrometry
ESOF	Euroscience Open Forum
EU	European Union
EVI	European Vaccine Initiative
EVRI	European Vaccine Research & Development Infrastructure
EWIV	Europäische Wirtschaftliche Interessensvereinigung
FDA	Food and Drug Administration
FP	Framework Programme
FR	France
GADI	Global Adjuvant Development Initiative
GB	Gabon
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
GH	Ghana
GIA	Growth Inhibition Assay
GLA-SE	Glucopyranosyl Lipid Adjuvant-Stable Emulsion
GM	The Gambia
GMP	Good Manufacturing Practice
GPI	Glycosylphosphatidylinositol
GSK	GlaxoSmithKline
HA	Haemagglutinin
HEK	Human Embryonic Kidney cells
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HTF	Danish National Advanced Technology Foundation
HuHep	Functional Human Liver Cells
HZI	Helmholtz Centre for Infection Research
IB	Investigator's Brochure
iBET	Instituto de Biologia Experimental e Tecnológica
ICGEB	International Centre for Genetic Engineering and Biotechnology
ICH	International Conference on Harmonisation
ICS	Intracellular Staining
IDEA	Dissecting the Immunological Interplay between Poverty Related Diseases and Helminth Infections: An African-European Research Initiative
IDRI	Infectious Disease Research Institute
IDT	IDT Biologika GmbH
IE	Republic of Ireland
IFA	Immunofluorescence Assay
IFN	Interferon
IFNγ	Interferon Gamma
IHI	Ifakara Health Institute
IL	Interleukin
IMB	Irish Medicines Board
IMPD	Investigational Medicinal Product Dossier

InnoMalVac	Optimising antigen production and selection for a vaccine against blood-stage Pf malaria based on PfRH5
Inserm	Institut national de la santé et de la recherche médicale
Intravacc	Institute for Translational Vaccinology
INTS	Institut national de transfusion sanguine
IP	Intellectual Property
IPROVE	Innovation Partnership for a Roadmap on Vaccines in Europe
IRB	Institutional Review Board
ISAC	Independent Scientific Advisory Committee
IT	Italy
IVR	Initiative for Vaccine Research
IWH	Internationale Wissenschaftsforum der Universität Heidelberg
kDa	kilo Dalton
KE	Kenya
KEMRI	Kenya Medical Research Institute
KfW	Kreditanstalt für Wiederaufbau
KHRC	Kintampo Health Research Centre
LSHTM	London School of Hygiene & Tropical Medicine
M. tuberculosis	*Mycobacterium tuberculosis*
MALDI-MS	Matrix-Assisted Laser Desorption Ionisation Mass Spectrometry
Matrix M	Adjuvant by Novavax, in which matrix complexes are formed by a specific mixture of Quillaja saponin, cholesterol and phospholipids
MBR	Master Batch Record
MCB	Master Cell Bank
ME-TRAP	Multiple Epitope Thrombospondin-Related Adhesion Protein
MF59	Novartis Vaccines' proprietary adjuvant, the first oil-in-water adjuvant to be commercialised in combination with a seasonal influenza vaccine
MIM	Multilateral Initiative on Malaria
MPIIB	Max Planck Institute for Infection Biology
MRC	Medical Research Council
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSP	Merozoite Surface Protein
MTCT	Mother-To-Child Transmission
MVFG	Malaria Vaccine Funders Group
MVTR	Malaria Vaccine Technology Roadmap
MULTIMALVAX	Multistage Malaria Vaccine
MVA	Modified Vaccinia Virus Ankara
MVDAS	Modern Vaccines, Adjuvants & Delivery Systems
MVI	Malaria Vaccine Initiative
MVVC	Malaria Vectored Vaccines Consortium
MVVC 2	Malaria Vectored Vaccines Consortium 2
MVW	Malaria Vaccine for the World
NA	Neuraminidase
NF54	Pf line derived from patient isolate near Schiphol Airport, Amsterdam; parasite presumed to be of West African origin
NHP	Non-Human Primate

NHRC	Navrongo Health Research Centre
NHS	National Health Service
NI	Nigeria
NIBSC	National Institute for Biological Standards and Control
NID	Neglected Infectious Disease
NIH	National Institutes of Health
NL	The Netherlands
P27A	Fragment P27A of the novel malaria protein PFF0165c
P27A-CTB	Safety and immunogenicity of P27A, a novel candidate blood-stage malaria vaccine, in malaria exposed African adults
PAM	Pregnancy-Associated Malaria/Placental Associated Malaria
PAMCPH	Recombinant var2CSA protein as a vaccine candidate for pregnancy associated malaria
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PDP	Product Development Partnership
PE	*Plasmodium falciparum*-infected Erythrocytes
PEGS	Protein Engineering Summit
PEI	Paul-Ehrlich-Institute
Pf	*Plasmodium falciparum*
PfEMP1	*Plasmodium falciparum* Erythrocyte Membrane Protein-1
PfPEBS	*Plasmodium falciparum* Pre-Erythrocytic and Blood Stage
PGE	Prostaglandin
PhD	Doctor of Philosophy
PIM	Paratyphoid Infection Model
PlacMalVac	Clinical development of a var2CSA-based placental malaria vaccine candidate
PM	Placental Malaria
PPD	Purified Protein Derivative
PRD	Poverty-Related Disease
PRIMALVAC	Recombinant var2CSA protein as vaccine candidate for pregnancy associated malaria
PT	Portugal
QC	Quality Control
QP	Qualified Person
qPCR	Quantitative Polymerase Chain Reaction
R&D	Research and Development
R21	Circumsporozoite protein particle
RCSI	Royal College of Surgeons Ireland
REC	Research Ethics Committee
Rh5	Reticulocyte-binding Protein Homologue 5
RIVM	National Institute for Public Health and the Environment
RoA	Return on Assets
RNA	Ribonucleic Acid
RTS,S	The RTS,S vaccine was engineered using genes from the repeat and T-cell epitope of Pf malaria CSP, a hepatitis B virus envelope protein

	(HBsAg) and a chemical adjuvant to boost the immune response
S2	Schneider 2
S. aureus	*Staphylococcus aureus*
S. typhi	*Salmonella enterica* serovar Typhi
S. paratyphi A	*Salmonella enterica* serovar Paratyphi A
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SDS-PAGE	Sodium Dodecylsulphate Polyacrylamide Gel Electrophoresis
SE	Stable Emulsion
SEC	Science and Ethics Committee
SFU	Spot-Forming Unit
Sida	Swedish Development Agency
SME	Small/Medium-sized Enterprise
SN	Senegal
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
SSI	Statens Serum Institute
SWE	Stable Water Emulsion
Swiss TPH	Swiss Tropical and Public Health Institute
TB	Tuberculosis
TBVI	TuBerculosis Vaccine Initiative
TLR	Toll-Like Receptor
TNA	Transnational Access
TRANSVAC	European Network of Vaccine Research and Development
TZ	Tanzania
Tzm-bl	A frequently used HIV-1 reporter cell line developed from HeLa cells (a human cervical epithelial carcinoma cell line)
UCAD	Universite Cheikh Anta Diop
UCPH	University of Copenhagen
UHEI	University of Heidelberg
UK	United Kingdom
UNIL	University of Lausanne
UOXF	University of Oxford
uPA	Urokinase Plasminogen Activator
US	United States
USA	United States of America
USP	User Selection Panel
UVRI	Uganda Vaccine Research Institute
Var	Genes encoding the PfEMP-1 proteins
VFL	Vaccine Formulation Laboratory
VLP	Virus-Like Particle
VP	Viral Particle
VSCR	Vienna School of Clinical Research
WHO	World Health Organization
WP	Work Package

FOREWORD

Clemens Kocken, Chairman of EVI European Economic Interest Grouping Board

I first became involved with the EVI Board in 2010, as a representative of the Biomedical Primate Research Centre (BPRC) in the Netherlands when it joined the European Economic Interest Grouping, the overarching governance body of EVI. In the few years since then, EVI has grown and diversified, and although it is still committed to malaria, it is also venturing into other diseases of poverty, in line with its mandate. I have chosen to mention just three projects here, which commenced in 2013, but this is by no means an all-inclusive list.

Starting with malaria, good progress is being made in two projects involving Pregnancy Associated Malaria vaccine candidates. The selection of candidate antigens has been finalised and process development is underway. EVI has recently become involved in a new technology, the immune-enhancing antigen IMX313, which is being assessed as a vaccine against the emergence of highly antibiotic-resistant strains of *Staphylococcus aureus*. This new technology could greatly enhance the development of malaria vaccine candidates. Finally, I am naturally proud of BPRC's development of a "universal" influenza vaccine candidate, which can provide broad coverage against different strains, in a project coordinated by EVI. This approach is based on the lessons learnt from the development of our in-house malaria vaccine candidate, AMA1-DiCo.

In 2013, we also saw the publication of the European Vaccine Research and Development Infrastructure Roadmap developed by EVI together with the scientific community.

A positive external review took place last year, emphasising the very low management costs, which contributes to an excellent return on investment. On the basis of this review, Irish Aid confirmed its continued financial commitment to EVI.

I hope you will find the content of the Annual Report both informative and enlightening. EVI is unique in Europe, its mission is important, its performance is proven, and it deserves the attention of public and private funders interested in making a real difference to the health of people in the developing world.

Executive Summary

EVI was established in 1998 as the EMVI, and in 2013 we therefore celebrated our 15th anniversary. We were fortunate that, during this anniversary year, several projects achieved major development milestones. Furthermore, the launch of new and innovative projects allowed EVI to venture into novel areas.

Regarding EVI-funded projects, both AMA1-DiCo and P27A received approval from the regulatory authorities to proceed to phase Ia/b clinical trials, which will commence during first quarter of 2014. Among the projects focusing on the development of vaccines against PAM, PRIMALVAC continued its successful preclinical development and PAMCPH progressed towards the manufacture of the vaccine candidate, which will be tested later in a phase I clinical trial. Finally, the CSVAC project was officially completed in July.

In terms of EC and EDCTP funding awarded to EVI, the highlights of 2013 include the following projects:

MVVC: The phase IIb adult efficacy clinical trial was completed at KEMRI and UCAD. The KEMRI phase IIb efficacy data are promising and have been submitted for publication.

TRANSVAC: This infrastructure project concluded successfully in September. A roadmap was developed during the project to establish a European vaccine R&D infrastructure, and this was presented to a diverse and interested audience at a final stakeholders' workshop.

The following new EC projects began in 2013:

BELLEROPHON uses an innovative tagging strategy that promotes antigen oligomerisation. Its ultimate objective is to create an entirely novel vaccine against *Staphylococcus aureus* infections in humans.

EDUFLUVAC will use a combinatorial immunisation strategy to develop a universal influenza vaccine that aims to "educate" the immune system and thus confer better protection against epidemic influenza.

IPROVE is a new policy project that aims to develop a roadmap to guide strategic decisions on the future of vaccine research and development in the EU.

The third EVI Rendez-Vous took place on 4 December 2013 in Heidelberg. As in previous years, EVI presented its current project portfolio and the audience (comprising partners, collaborators and other colleagues) was eager to learn about our recent progress.

We hope that the current year sees continued success in our diverse project portfolio.

Odile Leroy, Executive Director

THE YEAR IN GENERAL

General

In 2013, EVI celebrated its 15th anniversary, an important milestone in its history that was marked with a symposium on global health and diseases of poverty, held under the patronage of the regional Minister for Science, Research and the Arts, Theresia Bauer.

Fundraising

EVI also successfully mobilised significant resources from different funding bodies to support its activities in 2013. Importantly, the long-standing EVI donor, Irish Aid, confirmed its further commitment, in recognition of the quality and importance of EVI's work. This was highlighted by an external review carried out by America Appraisal, thereby demonstrating the trust placed in EVI. In addition, the EC awarded EVI with funding for four new projects. The total amount raised by EVI and its partner organisations was €16,577,889.

EVI Vaccine Projects

Two new vaccine R&D projects were launched in 2013, both with co-funding from the EC. EDUFLUVAC uses a combinatorial immunisation strategy similar to the AMA1-DiCo approach for malaria vaccine with in this case the aim to develop a universal influenza vaccine that confers better protection against epidemic influenza. If successful, the universal influenza vaccine would offer a tremendous advantage because it would eliminate the need for a seasonal vaccine and annual vaccination campaigns. The BELLEROPHON project uses an innovative tagging strategy that promotes the oligomerisation of antigens. Although this project focuses on the development of a vaccine against *Staphylococcus aureus* infections in humans, the same technology could be used in the future to increase the immunogenicity of vaccines against malaria and other diseases of poverty.

In the PAMCPH project, adjuvant formulation studies were carried out and subsequent preclinical work in animals was initiated to select the best adjuvants for the clinic. In the PRIMALVAC project, cell line development was completed and the reproducibility of a new fermentation process was assessed. The upstream process is ready for transfer to a CMO, and the development of the downstream process was initiated at the end of the year.

Regarding other projects funded by EVI, the IMPD for P27A was submitted to the Swiss regulatory authorities who, after minor revisions, authorised the project team to proceed with a phase Ia clinical trial in Switzerland in November. The first immunisation is scheduled for the first quarter of 2014. Similarly, the clinical trial for AMA1-DiCo was approved by the French regulatory authorities in November. The first immunisation in the phase Ia/Ib AMA1-DiCo clinical trial was scheduled for January 2014 in France.

The CSVAC project concluded in 2013 with a successful phase Ia clinical trial to determine the safety and immunogenicity of the *P. falciparum* CSP in ChAd63 and MVA replication-deficient viral vectors. The vaccine combination was safe and well tolerated, and the results of the ELISpot assays showed that both doses of the vaccine candidate were immunogenic and induced high-level T-cell responses.

In the MVVC project, which involves a series of clinical trials, the phase IIb adult efficacy trial was completed at KEMRI and UCAD. The Kenyan phase IIb efficacy data are very

promising and have been submitted for publication. Data analysis for the UCAD phase IIb clinical trial and other clinical trials in the same project are currently underway.

Cross-cutting Activities

TRANSVAC was successfully completed in September. The final annual meeting took place in Heidelberg at the beginning of the year, and a final stakeholder workshop was organised to present the roadmap for the establishment of a European vaccine R&D infrastructure that was developed as part of the project. EVI was also strongly engaged in securing funding for a follow-up project to TRANSVAC.

The IPROVE project is a new policy project funded by the EC, aiming to establish a clear vision of the priority innovations and technologies in immunisation which are necessary to address infectious and non-infectious diseases that threaten public health in Europe and beyond.

EVI Rendez-Vous

EVI's third Rendez-Vous took place in Heidelberg on 4 December 2013. The EVI project portfolio was presented to a lively audience comprising partners, collaborators and other colleagues.

Governance

The EVI Board approved Alister Craig (Liverpool School of Tropical Medicine, UK) as the chair of the EVI SAC. Ingileif Jónsdóttir (Landspitali University Hospital and Faculty of Medicine, University of Iceland), and James Robertson (until his recent retirement, Principal Scientist at the Division of Virology, National Institute for Biological Standards and Control (NIBSC), UK), were approved as new EVI SAC vice-chairs. Clemens Kocken (BPRC, The Netherlands) was nominated as the new chair of the EVI Board.

INTRODUCTION

Malaria vaccines that prevent mortality and morbidity: blood-stage vaccines

Clinical malaria occurs when malaria parasites from the genus *Plasmodium* invade red blood cells (the blood stage of the infection). Immunological studies in humans and animals have demonstrated that the immune response induced by blood-stage antigens can protect against the disease. Most antigens currently used as vaccine candidates are merozoite antigens. EVI has developed several blood-stage antigens with the intention of combining them in a second generation of malaria vaccines. The recent eradication push has brought the role of blood-stage malaria vaccines into question because they do not block transmission. However, studies in humans and animals have shown that controlling the parasite density can reduce the generation of gametocytes in the blood stream, and thereby also limit transmission.

Antigenic diversity is another challenge for the development of blood-stage vaccines. Ideally, candidate vaccines should be based on less polymorphic and more conserved antigen domains. Approaches to address this challenge include the development of recombinant antigens (AMA1-DiCo, MSP1 and EBA175), synthetic peptides (P27A) and antigens expressed on viral vectors (ME-TRAP and AMA1).

AMA1-DiCo

Partners

Biomedical Primate Research Centre, NL

Centre d'Investigation Clinique en Vaccinologie Cochin-Pasteur, FR

Centre National de Recherche et de Formation sur le Paludisme, BF

Confarma, FR

European Vaccine Initiative, DE

Fraunhofer IME, DE

Gregory Fryer Associates Ltd, UK

Henogen Novasep, BE

Infectious Diseases Research Institute, USA

Institut national de la santé et de la recherche médicale, FR

NNE Pharmaplan GmbH, DE

Nova Laboratories, Ltd, UK

Output Pharma, DE

AMA1 is a leading vaccine candidate against *P. falciparum*. Recombinant proteins representing the whole ectodomain (domains I–III) of *P. falciparum* AMA1 can induce antibodies that recognise native parasites and inhibit the invasion of erythrocytes by merozoites in vitro.

To investigate the role of human antibodies in naturally-acquired immunity, children in three separate endemic populations were tested for reactivity prior to the malaria transmission season and to determine whether or not they suffered an episode of malaria during 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, based on univariate analysis after adjusting for age. In one of the Kenyan cohorts and a separate Gambian cohort, antibodies to domain II were also associated with protection. However, the protective associations were only seen among Kenyan subjects that were positive for the parasite during pre-season serum sampling, a phenomenon noted in previous studies of Kenyan cohorts with antibodies against the infected erythrocyte surface. Antibodies to

domain III were very rare in all populations. These 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 of PfAMA1 FVO [25-545] was produced under cGMP[1]. The product was evaluated in a phase I clinical trial with three different adjuvants: alhydrogel, GSK's AS02A and Montanide ISA720. The results were very promising, with average growth inhibition levels of up to 50% when higher vaccine dosages were combined with AS02A and Montanide ISA720[2].

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

The limited polymorphism of PfAMA1 enabled the design of three artificial PfAMA1 sequences with a very high coverage of naturally-occurring alleles (on average > 97%). This DiCo approach, recommended by the SAC and approved by the Board in October 2008, is expected to overcome the polymorphism found in nature, promoting a broad response to all naturally-occurring AMA1 alleles. These expectations have been met in immunogenicity studies using both rhesus monkeys and rabbits. The total budget available for the development of an AMA1-DiCo vaccine is up to €5,206,111.

The EVI-funded development of an AMA1-DiCo vaccine candidate has now moved to active clinical development. A positive opinion was given by the French and Burkinabe ethics committees and the sponsor received the regulatory green light to proceed with the phase I arm in France. Immunisation with AMA1-DiCo in the phase Ia arm began during the first quarter of 2014 in CIC-Cochin, Paris, and will be followed by the phase Ib arm in the second quarter of 2014 at CNRFP, Burkina Faso.

P27A

Partners

ALMAC Sciences, UK
Centre Hospitalier Universitaire Vaudois, CHCiToxLAB, FR
European Vaccine Initiative, DE
Gregory Fryer Associates Ltd, UK
Ifakara Health Institute, TZ
Infectious Diseases Research Institute, USA
Nova Laboratories, Ltd, UK
Output Pharma, DE
University of Lausanne, CH

Preclinical validation of P27A was approved in 2013. This vaccine candidate is an intrinsically unstructured, hydrophilic fragment of the *P. falciparum* malaria protein PFF0165c, 104 amino acids in length[3], which was submitted in 2007 by Professor Giampietro Corradin, UNIL. It was not originally recommended for funding by the SAC, but a six-month contract to evaluate this candidate with various adjuvants was signed with UNIL in September 2008 in accordance with a Board decision to help improve certain proposals. A successful proposal was

[1] Faber et al. Vaccine 2008.08.55

[2] Roestenberg, Plos One 2008

[3] Olugbile S. et al., Infection and Immunity

submitted in response to the call in December 2008. The total budget for the development of P27A is up to €1,385,450.

The inhibition of both merozoite invasion and monocyte triggering by antibodies in ADCI were investigated while using genome mining to search for novel vaccine candidates. First we considered naturally-occurring antibodies in individuals with acquired protection following exposure to the malaria parasite, and later we also considered antibodies induced by immunisation with different candidates. From a series of 95 polypeptides representing novel and unexplored alpha helical coiled coil segments of *P. falciparum* blood-stage proteins, the screening process focused on 18 novel antigenic genes that were recognised by antibodies in exposed populations. Affinity-purified antibodies were studied in GIAs and ADCI assays, revealing that antibodies specific to 11 peptides totally or partially interrupted the intra-erythrocytic development of *P. falciparum*. This occurred solely in cooperation with blood monocytes and no direct effect was observed[4].

These results support passive transfer experiments showing that total immunoglobulin from protected individuals passively transferred into naïve recipients acts predominantly through a monocyte-dependent, antibody-mediated mechanism. The vaccine candidate discussed here was selected following a series of sequential screens that highlighted P27A as the target of an immune response with satisfactory characteristics for vaccine development[5].

The EVI-funded P27A vaccine candidate was recently moved into active clinical development. For the P27A phase Ia/Ib clinical trial, the project team received ethical clearance and authorisation to begin the phase Ia arm of a first-in-human clinical trial at CHUV in Switzerland. Immunisation began in the first quarter of 2014 followed by the phase Ib arm in the second quarter of 2014, at IHI in Tanzania.

MVVC

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 (acquired by GlaxoSmithKline in May 2013)

Université Cheikh Anta Diop, SN

University of Oxford, UK

Vienna School of Clinical Research, AT (until 31 Jan 2013)

MVVC is funded by EDCTP in response to the 2008 call "Malaria Vaccines Integrated Project – Clinical Trials / Capacity Building / Networking". The total funding provided by EDCTP is €5,613,936. This is complemented by co-funding from the Irish Aid Department of Foreign Affairs, Sida, MRC UK, the Federal Ministry of Science and Research, Austria and third-party contributions from all the project partners, making a total budget of €9,514,711. The project is scheduled to last for four and a half years (2009-2014).

[4] Villard et al., 2007

[5] Olugbile et al., 2009

The MVVC consortium includes four African partners and initially four European partners, with EVI as the coordinator. The collaborators and partner institutions were selected according to the proposed objectives of the consortium and the collective expertise they offered for the mutual benefit of all partners. UOXF sponsors the clinical trials and has developed and manufactured the vaccine candidates. Okairos, which was acquired by GlaxoSmithKline in May 2013, specialises in the development and production of adenovirus-based vaccines. VSCR provided and coordinated training courses for the MVVC consortium. Three of the African partners (CNRFP, KEMRI, and MRC) are experienced in clinical trials, and the fourth (UCAD) has set up clinical trials infrastructure and thus provides the facilities for the malaria vaccine clinical trials. The main objective is to demonstrate 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. This will be achieved by integrating capacity-building and networking in the design and implementation of phase I and II clinical trials of malaria vaccine candidates delivered using viral vectors, in East and West African adults, children, and infants.

Its specific objectives are listed below:

- To demonstrate the safety and immunogenicity of a ChAd63 and MVA prime-boost regime encoding the ME-TRAP malaria antigens, in adults and young children in sub-Saharan Africa.
- To assess the efficacy, safety, and immunogenicity of this new prime-boost regime in protection against clinical malaria in adults and children at multiple sites in East and West Africa.
- To ensure continued maintenance and further consolidation of the well-established sites at level 4 and to assist in the upgrading of the less-established sites from levels 1, 2 or 3 to level 3 or 4 investigational sites by the end of MVVC.
- To develop clinical trial capabilities, infrastructure and human resources that ensure the sustainability of the investigational sites after the end of the project.
- To develop the partners in the consortium into a well-established network using the already existing collaboration as a baseline for further development.
- To establish relationships with existing like-minded networks external to MVVC by using the partners' numerous existing networks, specifically encouraging South-South and North-South partnerships.

The phase IIb clinical trials in KEMRI and UCAD were completed in 2013 and the results of the phase IIb clinical trial at KEMRI showed encouraging preliminary evidence of efficacy. The phase IIb clinical trial to assess the efficacy of the ChAd63/MVA ME-TRAP vaccine candidates in Burkinabe children aged 5–17 months commenced at the beginning of 2013 and the last booster milestone of the last subject was reached in August.

MVVC 2

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 (acquired by GlaxoSmithKline in May 2013)

Université Cheikh Anta Diop, SN

University of Oxford, UK

Vienna School of Clinical Research, AT (until 31 Jan 2013)

Novartis Vaccines and Diagnostics, IT

Kintampo Health Research Cemtre, GH

MVVC 2 is a two-year project coordinated by the EVI, building on the MVVC project which started to establish a strong network between four African partners and collaborators in Europe. This network was enlarged to include two new partners, and capacity-building efforts will be expanded during the course of MVVC 2.

MVVC 2 is funded by EDCTP in response to the December 2011 call "Field Trials of a New Combination Malaria Vaccine in West African Adults and Children (MVVC 2)". The EDCTP grant is complemented with co-funding from EU Member States, BMBF, Irish Aid, MRC UK, Sida and third-party contributions, with a total project budget of approximately €1,239,153. The MVVC 2 consortium includes five African partners and initially five European partners.

The project aims to determine whether the vectored prime-boost malaria vaccines are compatible with the EPI vaccination schedule and whether the addition of a CSP particle in the adjuvant will enhance the efficacy of vectored prime-boost vaccines. The safety and immunogenicity of the vectored liver-stage malaria vaccine candidates co-administered with EPI vaccines will be assessed in Gambian infants. The safety, immunogenicity and efficacy of the CSP particle in the adjuvant, alone and combined with the vectored malaria vaccine candidates, will be assessed in African adults.

As part of the integrated strategy, capacity building and networking activities will be used to strengthen the clinical trial and laboratory capabilities of the African sites, allowing them to conduct the proposed clinical trials and other health research.

The MVVC 2 consortium held its kick-off meeting in January in Dakar, Senegal, and started preparing for the clinical trials at MRC, The Gambia, and CNRFP, Burkina Faso. The KHRC site was assessed and the site was recommended for further activities, including an immunology capacity-building plan to strengthen its cellular immunology capabilities.

InnoMalVac

Partners

European Vaccine Initiative, DE

University of Oxford, UK

ExpreS2ion Biotechnologies, DK

There are currently no PfRH5-based vaccine candidates in clinical development, but it has now been demonstrated that immunisation with full-length PfRH5 antigen is required to induce protective cross-strain antibodies.

The malaria group at the Jenner Institute, UOXF, has recently secured EC FP7 funding (MultiMalVax) to advance PfRH5-based adenovirus-poxvirus vectored vaccines into phase

I/IIa clinical trials. However, a protein-in-adjuvant vaccine is considered to be essential by downstream funders and industry in order to achieve the highest possible titres of protective antibodies, and this approach is also suitable for short-term re-boosting vaccinations (unlike recombinant viral vaccines which induce anti-vector immunity).

The InnoMalVac project aims to optimise and characterise the *Drosophila* S2 cell system for the production of full-length PfRH5 protein, before commencing technology transfer, process development and cGMP manufacture.

The project started in June 2013 and has progressed as anticipated, with some polyclonal S2 cell lines expressing different variants of the PfRH5 already established.

PAM vaccines

PAM is caused by parasite-infected blood cells binding to the placental receptor CSA, and their subsequent accumulation in the placenta, from where they can infect and ultimately kill both the mother and the child. Pregnant women are particularly vulnerable to this type of malaria because their immunity is reduced during pregnancy. Every year, more than 100 million pregnant women are threatened by PAM, and 80,000–200,000 children die from the infection every year[6]. This is a long-neglected health challenge, and currently there is no vaccine available to prevent PAM.

EVI has raised funds from BMBF, Inserm, the EC, and the HTF through UCPH, with further co-funding from Irish Aid, and has set up a collaboration with NIH. The three most advanced groups dealing with this target are therefore collaborating on the development of a PAM vaccine. The two ongoing projects offer hope for reducing the burden of malaria in pregnant women and improving the health of mothers and new-borns.

The target product profile for PAM vaccines differs from standard malaria vaccines. PAM vaccines target young adolescent girls before childbearing age, and the vaccination should be associated with other vaccines that prevent rubella or uterine cervical cancer caused by HPV. Depending on the other malaria vaccines available on the market, a PAM vaccine could potentially also be associated with a booster dose of regular malaria vaccine in adolescent girls.

The projects focus on the distinct form of the parasite that infects the placenta. Recent research supports the development of var2CSA as a leading candidate for the PAM vaccine[7]. This is a member of the PfEMP1 adhesins encoded by the *var* gene family, and is specifically expressed by placental parasites. Women acquire antibodies against var2CSA over successive pregnancies, as they become resistant to PAM[8]. These data suggest that vaccines based on var2CSA could help to block the adhesion of CSA-binding parasites to the placenta.

The 350-kDa var2CSA transmembrane protein has a 300-kDa extracellular region composed of six DBL domains and a cysteine-rich inter-domain, interspersed with short inter-domain regions. DBL3X is the principal target of inhibitory antibodies that prevent

[6] The impact of maternal malaria on newborns, T.K. Hartman et al., Annals of Tropical Paediatrics (2010) 30, 271–282

[7] Baruch et al., 1995; Su el al., 1995; Smith et al., 1995

[8] Fried et al., 1998

parasite adhesion to CSA[9]. Naturally-acquired antibodies, and those induced by vaccination against the domain between the N-terminal sequence and the DBL2X segment, target overlapping strain-transcendent anti-adhesion epitopes[10]. These data indicate that vaccines designed to block interactions between the parasite and CSA should be based on the N-terminal region of var2CSA.

PRIMALVAC

Partners

BIOTEM, FR
European Vaccine Initiative, DE
GTP Technology, FR
Infectious Diseases Research Institute, USA
Institut National de la Santé et de la Recherche Médicale, FR
ISCONOVA, SE please define
Pfenex Inc., USA
Voisin Consulting Life Sciences, FR

PRIMALVAC aims to develop a PAM vaccine to improve pregnancy outcomes. The main objective is to obtain proof of concept that var2CSA-based vaccines induce long-lasting or rapidly-boosted cross-reactive and inhibitory antibodies suitable for human use. Recombinant forms of var2CSA will be generated, and their immunogenic activity will be assessed, specifically their ability to elicit functional and cross-reactive antibodies against placental forms of the parasite. The candidate antigens that best meet strict immunogenicity criteria will be moved into preclinical and clinical development.
PRIMALVAC has a total budget of €6,864,000 provided by the BMBF through KfW, EVI, Inserm and the INTS. The project started in December 2011 and will last four years. The highlight of 2013 was the downselection of the var2CSA DBL1X-2X vaccine candidate produced in *E. coli*, which was moved into further preclinical and clinical development. Upstream process development was completed by the end of 2013.

PAMCPH

Partners

University of Copenhagen, DK
European Vaccine Initiative, DE
ExpreS2ion Biotechnologies, DK
CMC Biologics A/S, DK

The overall objective of PAMCPH is to enable the manufacture of a vaccine that protects both the foetus and mother against the adverse effects of malaria during pregnancy. The aim of the project is to define the optimal antigen and adjuvant formulation, show that it can be produced in a scalable manner and confirm that it is safe to use in animals. CMP (UCPH), a global leader in PAM vaccine development, has identified a complex protein candidate that is not compatible with traditional vaccine production platforms. The technology at ExpreS2ion Biotechnologies is ideal for the cost-effective expression of complex antigens, and CMC Biologics A/S has the technology and knowhow to scale up production and ensure compliance with cGMP, allowing the team to take this major step towards solving a significant health problem. The overall aim of this project is to support the production of a recombinant var2CSA vaccine under cGMP conditions, allowing it to be used in the clinical trial supported by the PlacMalVac project.

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[9] Avril et al., 2011; Dahlback et al., 2011

[10] Bordbar et al., 2011; Bigey et al., 2011

PAMCPH has a total budget of €2,000,000 and it is funded by the BMBF through KfW, with co-funding from UCPH through the HTF. The project started in September 2012 and the duration is four years. The main achievements in 2013 were the development of a S2 cell line expressing high levels of an untagged antigen and the development of a cGMP-compliant upstream process.

PlacMalVac

Partners
University of Copenhagen, DK
Expres2ion Biotechnologies, DK
Institut de recherche pour le développement, FR
European Vaccine Initiative, DE
Université d'Abomey-Calavi, BN
University of Tübingen, DE

Women, who have acquired immunity against malaria during childhood, nevertheless become susceptible to malaria again during their first pregnancies. Parasites accumulate in the placenta, where a combination of altered blood flow and expression of CSA provides a new niche for parasites to sequester. Fortunately, women can acquire immunity against PM and in malaria endemic areas the average birth weight is significantly higher among second and third- compared to first-born babies[11][12]. This relatively fast development of protection has raised the hope that a vaccine for PM can be developed.

In 2003, var2CSA was identified at CMP (UCPH) as the parasite protein which enable parasite accumulation in the placenta[13]. The aim of a var2CSA based PM vaccine is to induce antibodies that can hinder adhesion in the placenta followed by destruction of infected red blood cells in the spleen.

One objective of the project is to conduct a phase I clinical trial with the PM vaccine from PAMCPH. Another objective is the implementation of a field site and a protocol for a phase II clinical trial in African women.

PlacMalVac is funded by the EC FP7 and has an overall budget of €5,934,981. The project started 1 March and the duration is three years. The main achievements in 2013 were the signature of the grant agreement in January, the kick-off meeting held in Copenhagen in April as well as the sponsor and Benin phase Ib site assessment.

Vaccines that prevent infection: liver-stage vaccines

Liver-stage or pre-erythrocytic vaccine strategies are designed to induce an immune response that neutralises the sporozoites and prevents their invasion of hepatocytes. This

[11] Brabin BJ. An analysis of malaria in pregnancy in Africa. Bull World Health 1983;61(6):1005-16.

[12] McGregor et al. Malaria Infection of the Placenta in the Gambia, West-Africa - Its Incidence and Relationship to Stillbirth, Birth-Weight and Placental Weight. Transactions of the Royal Society of Tropical Medicine and Hygiene 1983;77(2):232-44.

[13] Salanti A et al. Selective upregulation of a single distinctly structured var gene in chondroitin sulphate A-adhering Plasmodium falciparum involved in pregnancy-associated malaria. Mol Microbiol. 2003 Jul;49(1):179-91.

is typically a vaccine for travellers because it would prevent the advent of clinical disease if completely efficacious. A partially efficacious pre-erythrocytic vaccine would also be expected to reduce the incidence of new blood-stage infections.

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 main objectives were to produce a recombinant form of ChAd63 using a gene encoding most of the CSP (full length minus the GPI anchor sequence) and a recombinant MVA based on the same insert, then to achieve the cGMP manufacture of the vaccine candidates and carry out a dose-escalation phase Ia clinical trial to assess the safety and immunogenicity of ChAd63 CSP and MVA CSP in humans. Process development and cGMP production were supervised by UOXF and the phase Ia clinical trial was carried out at RCSI. UOXF acted as the sponsor of the clinical trial. The total CSVAC budget was up to €1,161,000.

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

CSP has also been used as a vaccine candidate in combination with an alternative delivery system based on the non-replicating ChAd63 vector along with a heterologous MVA boost. This new vaccine candidate could also, in later clinical trials, be combined in sequence with the current RTS,S/AS02D vaccine to produce stronger and longer-lasting immunity. Alternatively, and more readily, it could be combined with other ChAd63 and MVA vectors encoding ME-TRAP, MSP1 and AMA1, which are being developed with support from EMVDA, MRC UK, the Wellcome Trust and others.

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, for the induction of effector T cell and memory T cell responses. In pre-clinical models of malaria, there is extensive evidence that T cells recognising 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. Immunological correlates of immunity induced by the RTS,S/AS02 vaccine in phase IIa sporozoite challenge studies and in a recent clinical trial in Mozambique have shown 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 after vaccination is modest (~150 SFU per million PBMCs as determined by ELISpot).

All vaccinations were completed by the end of 2012, and only the follow-up telephone calls for the last group of subjects remained to be completed in 2013. In addition, sample analysis and report writing was finalised during 2013. The project officially finished on 31 July 2013 after a no-cost extension in 2012.

All vaccinations, subject visits and ELISpot assays were carried out according to protocol. The ELISpot assay results showed that both doses of ChAd63 CS were immunogenic, inducing strong T-cell responses. The mean peak response two weeks after vaccination was 439 SFU per million PBMCs for doses of 5×10^9 and 5×10^{10} VPs. Peak responses to

MVA CS boosting were observed one week after vaccination, achieving 1947 and 1659 SFU per million PBMCs for ChAd63 CS doses of 5 x 10^9 and 5 x 10^{10} VPs, respectively, with a mixed $CD4^+$ $CD8^+$ phenotype. No statistical difference was observed between the groups in terms of SFU per million PBMCs.

Regarding the breadth of the CSP response, T-cell responses in all subjects were detected in multiple peptide pools spanning the entire CSP vaccine insert in the ex vivo IFN-□ ELISpot assay. Following the priming immunisation with ChAd63 CS, individual responses were detected across all pools with no apparent individual immunodominant region of the CS insert.

SPOROVAC

Partners

European Vaccine Initiative, DE
Ikafara Health Institute, TZ
Radboud University Nijmegen Medical Centre, NL
Sanaria Inc., USA
Swiss Tropical and Public Health Institute, CH
University of Maryland, USA
University of Oxford, UK

SPOROVAC was selected for funding by the EVI SAC and approved by the EVI Board in 2012. It has a total budget of up to €1,500,000 and aims to accelerate the development of a liver-stage vaccine, which will protect vaccinated individuals from malaria symptoms caused by the blood-stage parasite. The general approach is a CHMI with infectious sporozoites from a chloroquine-sensitive *P. falciparum* strain (NF54). This is combined with chloroquine prophylaxis, which targets only the blood-stage parasites.

Sanaria was audited for cGMP manufacturing and an ICH-GCP audit was carried out to determine their ability to sponsor the clinical trial in Bagamoyo, Tanzania. Sanaria and EVI have started to organise the harmonisation of the qPCR assay for parasitaemia after CHMI, following two face-to-face meetings in Lausanne, Switzerland (April) and in Washington DC, USA (November), in which a core group of interested parties set out the initial harmonisation actions to be explored in 2014. In February, Sanaria submitted a project amendment requesting a change of administration route to intravenous (IV) injection. Following concerns raised by the US FDA regarding the use of the 7G8 *P. falciparum* strain in the absence of complete biodistribution tests and a dose-finding study, Sanaria changed the initially anticipated heterologous challenge with 7G8 to a homologous challenge with NF54. After recommendations by the EVI SAC, the EVI Board decided that a study with a similar design to the SPOROVAC clinical trial (carried out in EKUT, Germany) must receive a positive evaluation by the PEI before the SPOROVAC project was allowed to continue. Delays in the submission of the clinical trial protocol to the PEI therefore delayed the SPOROVAC clinical trial in Bagamoyo. The start of the clinical trial was postponed to the first quarter of 2014. During the annual review of the project, the EVI SAC recommended that the SPOROVAC project should not start until the availability of the heterologous strain for the challenge. The Board decided to wait until mid-February 2014 before deciding on the termination of the project.

Malaria vaccines that prevent infection and morbidity/mortality: combination vaccines

The most effective malaria vaccines are likely to be based on a multi-stage product, i.e. a combination of antigens targeting several stages of the malaria parasite life cycle.

MultiMalVax

Partners
University of Oxford, UK
European Vaccine Initiative, DE
Novartis Vaccines and Diagnostics s.r.l., IT
Okairos s.r.l., IT (acquired by GlaxoSmithKline in May 2013)
Université Pierre et Marie Curie, FR

The aim of the EC FP7 MultiMalVax project, which started in October 2012 with a budget of €6,000,000, is to test a multi-stage malaria vaccine to the point of proof-of-concept phase II testing in Europe, prior to clinical trials in malaria-endemic areas. Remarkable advances in the design of vaccines against all four stages of the *P. falciparum* life-cycle now allow the testing of multi-stage multi-component vaccines for the first time, with strong chances of success.

These advances are:

i) The availability of a new vectored prime-boost vaccination regime based on the Okairos ChAd technology that has been found to induce exceptionally potent $CD8^+$ T-cell responses and high titres of antibodies against multiple malaria antigens;

ii) The development of an improved version of the leading partially-protective RTS,S sporozoite vaccine candidate, termed R21, that lacks the excess of carrier hepatitis B virus antigen in RTS,S;

iii) The use of a vector technology screen to identify the blood-stage antigen Rh5 as the first antigen to induce potent strain-transcending neutralisation of blood-stage parasites in vitro as determined by GIAs; and

iv) The demonstration that vector-induced antibodies against two mosquito-stage antigens can achieve 100% transmission blocking against field isolates of *P. falciparum* in Africa.

The project will undertake four phase I/II clinical trials to assess the pre-erythrocytic, blood-stage and mosquito-stage components individually, and then together, using state-of-the art immuno-monitoring, key functional assays for vaccine-induced immunogenicity, and sporozoite and blood-stage parasite challenges to measure efficacy prior to field testing.

This SME-led collaboration includes one SME, two universities, a global pharmaceutical company and EVI, and will provide complementary abilities to accelerate the development of this promising vaccine product.

The main achievement of the year 2013 was the generation and characterisation of the ChAd63 and MVA vectors expressing Rh5 and mosquito-stage antigens. These vectors were moved into cGMP production and will be available for a clinical trial in the second quarter of 2014. R21 protein particles combined with adjuvant showed strong immunogenicity in preclinical assays, and rapid progress has been made in process development for this product. The ISAC was also established with Bob Seder, Vasee Moorthy and Alister Craig as appointed members.

Universal influenza vaccine

Current influenza vaccines afford only limited protection against seasonal as well as pandemic influenza. As influenza viruses can accumulate three or four amino acid substitutions per year and frequently undergo antigenic changes to escape population immunity, vaccine composition must be updated regularly and new vaccines must be

administered on an annual basis. The development of a universal influenza vaccine that can provide broad coverage against different strains within a subtype or even across subtypes has thus become a key public health priority in both industrialised and low-and-middle-income countries.

EDUFLUVAC

Partners

Biomedical Primate Research Centre, NL
Central Veterinary Institute, NL
ETNA Biotech SRL, IT
European Vaccine Initiative, DE
Instituto de Biologia Experimental e Tecnológica, PT
National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare Products Regulatory Agency, UK
Redbiotec AG, CH

In order to address the problem of antigenic drift and annual vaccine reformulation, the EC FP7 EDUFLUVAC Consortium proposes to develop a combinatorial immunisation strategy to educate the immune system towards cross-recognition and coverage against antigenic drift during seasonal influenza virus exposure. The strategy, developed by Ed Remarque at BPRC, is based on the success of the DiCo approach used for the development of a new malaria vaccine candidate in the AMA1-DiCo project. With a budget of €4,647,149, EDUFLUVAC aims to develop a novel influenza vaccine candidate encompassing a combination of multiple influenza HA and/or NA antigenic variants within a single subtype. The project will test the hypothesis that this vaccine concept, using the proven, modern technology of baculovirus-derived VLPs, will elicit broad neutralising immunity that will confer longer-lasting and broader protection against multiple strains of influenza virus.
The antibody response is broadened because the increased relative concentration of common epitopes dilutes out strain-specific epitopes. This will be achieved by testing the ability of a combination of historic HA variants to protect against a variety of modern isolates. Thus, the overall strategy of the EDUFLUVAC project will be to select HA and NA antigens representing antigenic drift within relevant subtypes and generate baculovirus vectors expressing one or more HAs. VLPs will be tested in immunological studies using mice before the further selection of vaccine candidates. Proof of principle will then be demonstrated for the EDUFLUVAC strategy in challenge studies using ferret and non-human primate models. Furthermore, an optimised process suitable for the cGMP-compliant production of VLPs will be developed. The project will take note of new influenza vaccine regulatory guidance and will be geared towards the development of a complete IMPD ready for transfer into cGMP production for early-phase clinical testing. Finally, the generated knowledge will be disseminated through networking activities including targeted workshops.

The main achievements this year include the November project kick-off meeting at IWH, Heidelberg, Germany, and the selection of HA and NA antigens to be used to generate baculovirus vectors.

Paratyphoid vaccine

Systemic enteric fever in humans is often caused by *Salmonella typhi* and *Salmonella paratyphi A*, resulting in 27 million new cases worldwide and 200,000 deaths each year[14], with the highest number of cases in South and Southeast Asia. However, there are no vaccines against *Salmonella paratyphi A*, which is emerging as a major cause of pandemic enteric fever that is clinically indistinguishable from diseases caused by *Salmonella typhi*.

The limited investment in vaccine antigen discovery and the absence of defined correlates of protection for paratyphoid fever are holding back the development of strategies to prevent this disease. The step from early vaccine concepts to expensive field trials needs new and innovative approaches. Furthermore, as *Salmonella paratyphi* is a human-restricted pathogen, there is no animal model that allows the protective efficacy of vaccines to be evaluated.

PIM

Partners

European Vaccine Initiative, DE
University of Oxford, UK
Novartis Vaccines Institute for Global Health, IT
Wellcome Trust Sanger Institute, UK

The PIM project was selected for funding by the EVI SAC and approved by the EVI Board in 2013. The overall objective is to pursue advances that lead to the control of paratyphoid infection by improving the selection of vaccine candidates.

To advance the development of paratyphoid vaccines, PIM aims to develop the first controlled human model of paratyphoid infection that will provide a unique opportunity to study the immune response to *Salmonella paratyphi A*, identify potential correlates of protection and evaluate the efficacy of vaccine candidates by providing early proof of the vaccine concept.

This two-year project has a total budget provided by EVI of €325,000 complemented by co-funding from the BMGF.

The main achievement in 2013 was the cGMP manufacturing and release of the challenge strain of *Salmonella paratyphi A*.

New vaccine technologies

Staphylococcus aureus, including MRSA, is one of the most important bacterial pathogens responsible for skin lesions and deep infections. It causes approximately 16,000 deaths annually in Europe and 19,000 in the USA. Treatment is difficult and expensive and may require the prolonged intravenous administration of antimicrobials. The emergence of highly antibiotic-resistant *Staphylococcus aureus* strains, such as MRSA, is creating a serious global public health threat and an increasing economic burden. Because recent vaccine candidates against *Staphylococcus aureus* have not proven effective and therefore no vaccine is

[14] Buckle GC et al, J Glob Health, 2012

yet licensed by the US FDA or EMA, an efficient vaccine against this pathogen is urgently needed.

BELLEROPHON

Partners
University of Oxford, UK
Imaxio SA, FR
Preclin Biosystems AG, CH
European Vaccine Initiative EEIG, DE

BELLERROPHON is an EC FP7 project with a budget of €5,935,544, which commenced on 1 September 2013.

The aim of the BELLEROPHON project is to design, manufacture, and evaluate in a phase I clinical trial a novel *Staphylococcus aureus* vaccine candidate targeting both the cellular and humoral immune responses, and designed to protect against both MRSA and more sensitive *Staphylococcus aureus* strains.

The BELLEROPHON project comprises four European institutions involved in vaccine development, each contributing specialist expertise and technology. Imaxio, a French biotechnology company focusing on immunology, was the leader of the project application. The Jenner Institute (UOXF, UK) is an academic institution with key expertise in *Staphylococcus aureus* antigens and viral vector delivery systems, and is the project coordinator. EVI assists with project management and advises on cGMP production and clinical development aspects. The fourth member is Preclin Biosystems, a Swiss CRO with strong expertise in preclinical efficacy models for infectious diseases.

The main achievements in 2013 were the signing of the grant agreement in May and the consortium agreement in April. The kick-off meeting was held on 12-13 September, and was hosted by the coordinator in Oxford, UK.

Harmonisation and Services

IDEA

Partners

Centre Hospitalier Universitaire Vaudois, CH

Academisch Medisch Centrum bij de Universiteit van Amsterdam, NL

Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum, NL

Agence nationale de recherches sur le sida et les hépatites virales, FR

The 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

There is increasing recognition that NIDs represent a major public health burden with a particularly significant impact related to their widespread distribution across low-income countries. NIDs are caused by diverse infectious agents and predominantly by different types of worms, which are prevalent in tropical regions. Although most infections are asymptomatic, heavy infections result in significant morbidity. Despite limited intervention, population-based national programmes for the integrated control of worms have been scaled up over the last few years, following concerted advocacy and major philanthropic donations. These programmes raise important questions about the public health implications of co-infection and treatment for other diseases such as malaria, HIV/AIDS and TB[15]. Indeed there is growing epidemiological evidence for interactions between worms and these diseases. The most recent estimates indicate that approximately two billion people are infected with worms, 300,000,000 are severely affected and ~50% of cases are children. Infections include schistosomiasis and several species of intestinal worms also known as soil-transmitted helminths. WHO estimates that about 200,000 deaths are caused by schistosomiasis each year[16].

Given the considerable geographic overlap, co-infections of worms with HIV, TB and malaria affect tens of millions of people including children and adults. Preliminary epidemiological data from a small number of studies suggest that ~25% of those affected by HIV, malaria or helminth infections are co-infected. Although worm infections and HIV, TB and malaria have been studied extensively, the potential

[15] Eziefula 2008

[16] http://www.who.int/en/

impact of co-infections has been investigated only recently. First, the interaction between these diseases may increase the disease burden on society because effective vaccines are not yet available. Second, although worm, HIV, TB and malaria-specific immune responses have been the target of extensive investigations, the precise immune correlates of protection remain unknown for all these diseases. Third, there is no information about worm-induced immunity and its ability to modulate HIV, TB and malaria-specific immune responses. Fourth, there is limited knowledge concerning 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 because the limited available data suggest the effectiveness of vaccines is reduced in subjects with worm infections. IDEA is a five year EC-funded project with 20 consortium members coordinated by CHUV and has a total budget of €10,300,000.

The main achievement in 2013 for activities involving EVI was the selection of the investigational site UVRI to carry out two small stand-alone phase I clinical trials to study the influence of helminth infection on TB and HIV vaccine-induced immunity.

TRANSVAC

Partners

Biomedical Primate Research Centre, NL
Central Veterinary Institute, NL
Department of Health (former Health Protection Agency), UK
European Vaccine Initiative, DE
Helmholtz Centre for Infection Research GmbH, DE
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 types of diseases, there is currently very limited coordination between vaccine R&D groups, assay developers, and vaccine producers. Unarguably, the 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 objectives.

Any R&D group wishing to develop a new experimental vaccine must currently locate and approach a fragmented and non-harmonised group of vaccine development service providers on an individual basis.

TRANSVAC is an EC FP7 collaborative infrastructure project that ran from October 2009 until September 2013 with a total budget of €9,899,999. The project was a joint effort to unite European institutions and research groups in the field of vaccine development, and was coordinated by the EVI. TRANSVAC was designed to enhance European research and training, and to foster the seamless implementation of a permanent research infrastructure for early vaccine development in Europe.

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

The TRANSVAC project was completed in September and its main achievements are listed below:

- Free access to all TRANSVAC services including adjuvants, animal models, reference reagents, and global analysis platforms was provided to 29 vaccine projects with high potential, selected through a two-step peer-review process, first based on scientific excellence, and then on feasibility and impact. Since July 2012, TRANSVAC has also provided five additional infrastructures that may be accessed on a paid basis.
- TRANSVAC activities led to the rational development of novel vaccine formulations, reference standards, and new vaccine candidates (including the preparation of IMPDs for two vaccine formulations).
- Evaluation of vaccine candidates in different animal models (mice, humanised (HIS) mice, guinea pigs, pigs and non-human primates) combined with global analysis to gain insight into the mechanisms of action of the vaccines.
- Research for biomarkers including an intensive comparative analysis of Affymetrix and Agilent microarray data as well as Illumina RNA sequencing data for a BCG vaccination in a phase Ia clinical trial, harmonisation of SOPs for sample, microarray and data analysis, and the transcriptome mapping of samples from an HIV vaccine clinical trial in collaboration with the EuroNeut-41 project.
- Harmonisation and standardisation of assays have provided critical data for the choice of formulation, route of administration, vaccination dosages and schedules. SOPs for immunoassays in clinical trials are available and validated.
- To ensure the quality of assays that address vaccine specifications, 13 characterised malaria and TB antigens are available to external users.
- TRANSVAC also provides cell banks representing five new cell lines developed for the improved production of adenoviral vectors.
- TRANSVAC organised two highly successful modular courses in vaccine development, each attended by 15 selected external participants.
- Ten workshops were held on subjects as diverse as statistical analysis, animal models, global analysis, and discussion to strengthen collaborations between European vaccine R&D groups, assay developers, and vaccine producers.
- TRANSVAC experience has confirmed the need for a sustainable infrastructure for vaccine R&D. Representatives of vaccine manufacturers, biotechnology companies, academic research institutes, regulatory authorities, policy makers, and funding agencies have developed a roadmap setting out needs and gaps in European vaccine R&D infrastructure.

Policy

IPROVE

Partners
Vaccines Europe, BE
European Vaccine Initiative, DE
Sclavo Vaccines Association, IT
European Advanced Translational Research Infrastructure in Medicine, NL

IPROVE is an EC FP7 policy project, with a budget of €496,367 that aims to establish a clear vision of the priority innovations and technologies in immunisation required to address infectious and non-infectious diseases that threaten public health. IPROVE uses a bottom-up approach involving all key stakeholder groups in the European vaccine field to analyse the entire vaccine innovation chain, from the identification of needs and conceptualisation to vaccine discovery and development, including interventions necessary to improve education curricula, and vaccine perception and awareness by the public. The principal outcome of IPROVE will be a comprehensive roadmap to provide guidance for strategic decisions in future vaccine R&D in the EU. The project kick-off meeting was held in Brussels in December, where all project partners met to start the implementation of the work plan agreed upon for the next two years.

PRECLINICAL, PROCESS, PRODUCTION, IMPD

AMA1-DiCo

The IMPD has been finalised by EVI and submitted by the sponsor to the French regulatory authorities, ANSM. In October, ANSM asked for additional information to be included in the IMPD, and after the answers were provided by EVI, the clinical trial was approved in November. The AMA1-DiCo DP batch was certified for release to the clinical trial in December by the QP of Nova Laboratories Ltd. The long-term real-time stability analysis of the DP is underway.

InnoMalVac

UOXF has produced polyclonal S2 cell lines expressing seven different variants of PfRH5 (in collaboration with ExpreS2ion Biotechnologies). The development of purification strategies is underway and purified proteins have been characterised using different assays to select the best candidate.

MultiMalVax

ChAd63 and MVA vectors were generated for Rh5 and several mosquito-stage antigens (e.g. Pfs25 and Pfs230C), and multivalent vectors were also produced. Okairos produced Rh5 ChAd cGMP batches and the CMO IDT has finalised the manufacturing of the MVA Rh5 vector cGMP batch. Release testing is underway. R21 particles were produced for pre-clinical studies and show good immunogenicity. Process development is on-going, and R21 is expected to be available for clinical trials by mid-2014.

P27A

The IMPD was finalised by EVI and submitted by the sponsor to the Swiss regulatory authorities, Swissmedic. The IMPD was revised by EVI according to feedback from the regulators and the phase Ia arm of clinical trial P27A_1_13 was authorised to proceed in Switzerland in November. The P27A DP batch was certified for release to the clinical trial

in December by the QP of Nova Laboratories Ltd. The long-term real-time stability analysis of the DP is underway.

PAMCPH

UCPH and Expression Biotechnologies have selected a S2 producer cell line for the candidate antigen. A batch upstream process has been developed and the capture step for downstream processing has been selected.

In parallel, stability studies have been carried out in collaboration with the University of Kansas to define pH and temperature ranges at which the protein is stable. The CMO, CMC Biologics, has been selected and has received the cell line for MCB manufacturing in early 2014. Adjuvant formulation studies have been carried out and subsequent preclinical work in animals has commenced, to select the best adjuvants for the clinic. The development of analytical technologies is underway and will be completed in 2014.

PRIMALVAC

GTP Technology completed *E. coli* cell line development for the non-His-tagged selected candidate antigen. They also developed a fermentation process at the 50-litre scale and the process has been assessed for reproducibility. The upstream process is ready for transfer to a CMO. GTP Technology began downstream process development at the end of the year.

SPOROVAC

In March, the Sanaria GMP facilities in Rockville and corresponding manufacturing process were audited by EVI and an external consultant. During the second half of 2013, Sanaria manufactured two lots of the NF54 *P. falciparum* strain for administration in the planned clinical trial in Bagamoyo, Tanzania, and tested them in QC release assays. The production of a lot of the 7G8 *P. falciparum* strain began in October in preparation for heterologous challenge studies.

BELLEROPHON

In September, David Wyllie's group at UOXF began testing the immunogenicity of selected *Staphylococcus aureus* antigens with or without adjuvant. Meanwhile, Imaxio tagged the *Staphylococcus aureus* antigens with the proprietary Imaxio tag and also carried out preliminary immunogenicity assays. The selection and testing of different mouse models is currently underway.

TRANSVAC

Preclinical, Process and Production

The research component of TRANSVAC aims to promote and improve the use of molecular and cellular assays and standardised reagents, global analysis, adjuvants, animal models and cell banks specific to the development of experimental vaccines (see Delivery Platform section). Seven of the 15 TRANSVAC project work packages are dedicated to these aspects of vaccine development. In 2013, the following major results were achieved:

Production of recombinant vaccine candidates

Three additional recombinant vaccine candidates were selected from *M. tuberculosis*:

1. CFP10 (Rv3874, Lhp)
2. Esat6 (Rv3875, 6-kDa early secretory antigenic target Esat6)
3. PstS3 (Rv0928, PBP-3, PHOS2).

The LIONEX facility in Germany produced high-purity endotoxin-free lots of each candidate as confirmed by detailed QC analysis, SDS-PAGE, western blotting, host cell protein analysis, endotoxin measurement (LIONEX) and N-terminal sequencing/MALDI-MS/ESI-MS (HZI, Germany).

An MBR document was used to record process data and the results for each step. The document was hand filled and signed by the operator as is the general practice in a GMP facility. The filled MBR finally led to a batch record for the batch produced and stored at the LIONEX facility.

A total of eight recombinant vaccine protein candidates were produced by LIONEX for TB, malaria and HIV, followed by extensive QC as described above, confirming the identity of the proteins and the quality and purity of the product. The proteins were provided to users in several countries and can be provided to other users on request:

- HIV antigen: p24
- Malaria antigen: MSP-Fus
- TB antigens: ESAT6, CFP10, 16 kDa, 19 kDa, PncA, HSP70, HSP65, 85A, 85B, 85C, AlaDH, Apa, MPB83, Rv0251c, Rv1636, PstS1, PstS3.

Please contact info@lionex.de for further information.

Evaluation of vaccine candidates in different animal models

CVI optimised the pig influenza model for implementation in future studies. Several methods were used and/or optimised for the analysis of immune responses, and CVI developed a multiplex cytokine assay for this purpose. With these data, further research using pigs as a model for vaccine evaluation is now possible.

Published and unpublished data indicate that NHP macaque and rhesus spectrotypes may present with different manifestations or levels of disease following infection. The head-to-head approach chosen by the BPRC allowed the systematic and comprehensive analysis of adaptive T-cell and innate activated protein C response profiles, suggesting a gradient of responsivity amongst cynomolgus versus rhesus monkeys and amongst rhesus spectrotypes. Ultimately, the Indian type rhesus macaques used in this study were found to be more susceptible to *M. tuberculosis* infection, yet exclusively (partially) protectable by prophylactic BCG vaccination, compared to Chinese type rhesus macaques. Although genetic factors should not be over-interpreted when nurture and founder effects in NHP populations may be confounding, these findings nevertheless greatly contribute towards improved NHP cohort stratification and the refinement of preclinical NHP modelling.

Humanised mouse models have been optimised by HZI, allowing the generation of lymph nodes, increased cellular responses, and increased reconstitution levels of uPA mice (HuHep model) with human hepatocytes, promoting the efficient infection of HuHep mice with hepatitis B virus and hepatitis C virus. Multi-parametric flow cytometric readout systems have been developed using 13-16 colour panels which allow T cell subpopulations to be distinguished using a unique combination of surface markers. Animal models based on conventional mice have been developed in order to (i) characterise the strength and functionality of vaccine adjuvant candidates and (ii) understand the role of different immune cells in the elicitation of efficient immune responses.

Definition of biomarkers for protective immunity through the global analysis of host responses after vaccination

The samples from a phase Ia clinical trial with *M. bovis* BCG vaccination, using two different tuberculin skin test groups (PPD positive and PPD negative) were analysed in

more detail by Illumina sequencing at HZI. A clear distinction could be made between post-vaccinated PPD positive and PPD negative cohorts.

Indian and Chinese macaques and cynomolgus monkeys were also used for Illumina-based whole-transcriptome SNP identification at HZI, resulting in the species-dependent identification of SNPs (see *Evaluation of vaccine candidates in different animal models* above).

LIONEX analysed human blood samples from the EC FP7 EuroNeut-41 project, which aims to develop new vaccines that elicit neutralising antibodies to block HIV uptake into cells at mucosal sites and in the blood. A set of 166 blood samples provided by the University of Surrey was used for transcriptome analysis on the Affymetrix platform. The data were processed using the Partek Genomic Suite. The results will be made available in 2014, after the un-blinding of the samples.

Transnational Access Services

The TRANSVAC SAC and USP completed their evaluation of applications received in response to the TRANSVAC TNA services calls during 2013. A total of four user projects were selected in 2013 and have been given access to two types of services.

Users selected for the TNA calls for applications in 2013 (calls 1301-9 to 1304-10):

Study number	Applicant / User	Access granted to	Disease
1	Inserm, Lille, France Dr Camille Locht	Affymetrix Microarrays	Pertussis
2	King's College London, London, United Kingdom Dr Sandra Diebold	Affymetrix Microarrays	Ovarian carcinoma
3	University of Amsterdam, Amsterdam, The Netherlands Dr William Paxton	Stable Reference Reagents	HIV
4	Crucell, Leiden, The Netherlands Dr Jenny Hendriks	Stable Reference Reagents	Tuberculosis

tudy 1 focussed on the transcriptional response to vaccination with live attenuated *B. pertussis*, as part of an evaluation of a novel pertussis vaccination strategy in new-born children. Pertussis is still a major global public health issue. The aim was to develop a new vaccine to be administered at birth in order to provide early protection and prevent severe forms of the disease in new-borns. The attenuated *B. pertussis* strain BPZE1 was engineered by genetically altering or removing three toxins: pertussis toxin, tracheal cytotoxin, and dermonecrotic toxin. BPZE1 is non-pathogenic in mouse models, yet is able to colonise the respiratory tract and rapidly protect against *B. pertussis* challenge via TLR4 signalling. A phase I clinical trial showed that BPZE1 is safe in humans, yet able to colonise the nasopharynx and induce immune responses in all colonised subjects. However, not all subjects were colonised. This project compared the transcriptomes of colonised and non-colonised subjects as well as placebo controls in order to establish early and late transcriptomic profiles during the administration of BPZE1. RNA extracted from seven colonised subjects, seven non-colonised but vaccinated subjects, and seven placebo controls at all PBMC sampling time-points (i.e. 2–6 weeks before BPZE1/placebo administration, on the day of vaccination and 1, 2, and 4 weeks, and 5–6 months after

vaccination) were analysed on Affymetrix microarrays at the University of Regensburg (TRANSVAC service provider). These microarray data will help to evaluate the early and sustained immune responses in BPZE1-vaccinated subjects, leading to major publications in the field. The data will also allow the comparison of human and mouse models, for which similar transcriptomic approaches have been carried out in parallel.

Study 2 aimed to characterise the immunosuppressive tumour environment for the induction of anti-tumour immunity using TLR7/8 agonists, in the context of ovarian carcinoma. The long-term aim of this study is to develop a vaccine for the treatment of ovarian carcinoma based on antibody-mediated antigen delivery to dendritic cells in vivo. Monocyte-derived dendritic cells from healthy donors were generated and were treated overnight with the TLR7 agonist R848 in the presence or absence of ascites from ovarian carcinoma patients. To investigate the immunosuppressive role of IL-10 and PGE2, ascites depleted for these factors were compared to mock-treated ascites, resulting in 48 RNA samples derived from four independent experiments. The monocyte-derived dendritic cells were taken from three different healthy donors and were treated with the ascites fluid from the same two patients. The dendritic cells from one donor were also treated with the ascites fluid from two additional ovarian carcinoma patients. Initial analysis of the Affymetrix microarray data set (TRANSVAC service provider) revealed substantial donor variation in the gene expression profile of untreated monocyte-derived dendritic cells and R848-treated monocyte-derived dendritic cells. It is currently unclear why there is such a difference in the baseline gene expression of the monocyte-derived dendritic cells and why donors respond differently to R848. However, this has implications for the further analysis of the microarray data and it may be necessary to look at IL-10 and PGE2-dependent suppression of TLR7/8-mediated dendritic cell activation for each donor separately, which will require the generation of additional datasets.

Study 3 investigated HIV envelopes isolated from mother and infant pairs that were positive or negative for virus transmission. By comparing such differences it should be possible to map which genotypic differences in viral envelopes that undergo transmission can associate with phenotypes, and specifically neutralisation. The project tested viruses for neutralisation with a number of neutralising antibodies obtained from the NIBSC (TRANSVAC service provider). A well-established HIV-1 pseudo-typed neutralisation assay was used, based on the Tzm-bl cell lines and standard protocols. A number of reference antibodies were used to investigate the viral envelopes undergoing HIV-1 MTCT, aiming to improve the design of immunogens and induce potent neutralising antibodies targeting such viruses. The data generated in this project may guide vaccine development strategies involving the induction of strong neutralising antibody responses, or passive immunisation in pregnant women infected with HIV-1.

Study 4 aimed to standardise CMI assessment by flow cytometry for the development of an adenovirus-based TB vaccine candidate. A clinical trial is currently assessing AERAS-402/Crucell Ad35 which comprises a replication-deficient adenovirus serotype 35 (Ad35) vector modified to deliver TB antigens 85A, 85B, and 10.4. Adenoviruses are potent inducers of $CD8^+$ T-cell responses, which are considered an important component of immunity to TB and many other infections. The clinical trial is underway and peripheral blood lymphocyte samples from the clinical trial participants have been frozen and stored for the subsequent assessment of immune responses to the vaccine. For each ICS study, samples of the positive and negative control reference reagents from NIBSC (TRANSVAC service provider) will be included and treated in the same way as the clinical material. The ICS reference reagents will be used to monitor the performance of the primary assay used to assess the immunological responses to the candidate TB vaccine, which is based on

multicolour intracellular flow cytometry staining for cytokine expression. Access to the ICS reference reagents will improve the comparability and analysis of data obtained from these cells throughout the duration of the study. This will also ensure improved quality management of the assay process through the use of stable reference reagents. The data derived from this study (clinical immunological data, including the use of the ICS reference reagent) will be used to provide guidance for future clinical development plans.

DELIVERY PLATFORMS, ADJUVANTS AND VIRAL VECTORS

EVI has filled 3800 0.6-ml vials of aluminium hydroxide under cGMP conditions at Nova Laboratories Ltd to be used in all its preclinical and clinical trials. Please contact EVI at contact.us@euvaccine.eu for further information.

AMA1-DiCo

GLA-SE and aluminium hydroxide as a comparator will be used as adjuvants in the phase Ia/Ib clinical trial. EVI has purchased cGMP-grade GLA-SE and SE from IDRI, under a clinical supply agreement between EVI, Inserm and IDRI.

InnoMalVac

Rh5 is currently expressed as a recombinant protein in *Drosophila* S2 cells and the delivery system or adjuvant that will be used in the future has yet to be selected.

P27A

Two adjuvants will be used in the clinical trials: aluminium hydroxide as a reference adjuvant because it has shown good results in preclinical studies, and GLA-SE from IDRI. EVI has purchased cGMP-grade GLA-SE and SE from IDRI, under a clinical trial agreement between EVI, CHUV, IHI, IDRI and Swiss TPH.

PRIMALVAC

The selection of adjuvants is underway. The development plan will probably involve aluminium hydroxide as a comparator and one other adjuvant.

PlacMalVac

The selection of adjuvants is underway. The development plan will probably involve aluminium hydroxide as a comparator and one other adjuvant.

CSVAC

The malaria antigen CSP was delivered in a prime boost strategy using two different vectors: ChAd63 and MVA.

MVVC

The malaria antigen ME-TRAP was delivered in a prime boost strategy using two different vectors: ChAd63 and MVA.

MVVC 2

The malaria antigen ME-TRAP will be delivered in a prime boost strategy using two different vectors: ChAd63 and MVA. The adjuvant used to administer the CSP particles has yet to be selected.

MultiMalVax

The malaria antigens ME-TRAP, Rh5 and the transmission-blocking antigen will be delivered in a prime boost strategy by two different vectors: ChAd63 and MVA. The R21 CSP particle will be administered in adjuvants, probably MF59 and Matrix M.

BELLEROPHON

An innovative new tagging system (IMX313) from Imaxio will be used to enhance the immune response to selected *Staphylococcus aureus* antigens. When the tagged antigen is expressed, the IMX313 tag spontaneously auto-assembles into a heptamer, which indices a seven-fold aggregation of the antigen and thus enhances its presentation to the immune system. Imaxio has intiated the synthesis and immunogenicity testing of the tagged *Staphylococcus aureus* antigens.

EDUFLUVAC

The EDUFLUVAC project will use VLPs to deliver multiple influenza HA and/or NA antigenic variants. In 2013, the partners worked together to select the antigen strains that will be assembled in baculovirus vectors. In 2014, VLPs will be produced in insect cell lines by iBET, Portugal, using baculovirus vectors generated at Redbiotec AG, Switzerland.

TRANSVAC

Coherent development of novel and improved vaccine formulations and standards

A batch of each positive and negative lyophilised human PBMC sample ($CD4^+$ IFNγ) was produced as reference standards and made available for use in flow cytometry assays. A proof-of-concept study was completed to demonstrate the feasibility of IFNγ-encapsulated liposomes with a thermo-trigger release mechanism as a positive reference reagent for ELISAs. Two batches of purified and lyophilised Ag85A were produced with different formulations and made available for use in immunological assays. An anti-malaria (Pf) human serum standard was prepared and a biological study report was submitted to WHO ECBS for approval. The WHO ECBS has deferred the decision to their next meeting in October 2014. This reference standard is ready for distribution and will be available as a NIBSC reference reagent until it is accepted as a WHO International Standard of anti-malaria (Pf) human serum.

Development of cell line substrates for the production of viral vaccines

Two additional cell banks have been developed by UOXF:

- The 293 ADH cell bank was produced from a CBF working cell bank which, in turn, was prepared from the Bioreliance fully-tested MCB.
- The Procell92 ADH cell bank was derived from a CBF primary freeze vial which had been adapted back to adherent culture (more useful for generating virus starting material) from the Okairos-tested suspension MCB.

These cell banks of adherent HEK293 and Procell92 cells will allow partners to prepare pre-GMP starting materials for vaccines. External testing has confirmed the absence of mycoplasma. These are not fully certified cGMP banks.

In summary, the following cell banks were developed by UOXF during the TRANSVAC project and can be made available to external users on request:

- HEK293 cells for the production of recombinant adenoviral vectored vaccines.
- 911 MCB1 cells for the production of recombinant adenoviral vectored vaccines, with a lower risk of generating replication-competent viruses.

- 293 ADH cells with an adherent phenotype for the production of recombinant adenoviral vectored vaccines.
- Procell92S cells for the production of recombinant adenoviral vectored vaccines with tetracycline-regulated transgene expression during manufacture.

Please contact Prof Adrian Hill at adrian.hill@ndm.ox.ac.uk for further information.

CLINICAL DEVELOPMENT

EVI has selected clinical trial sponsors and investigational centres for several core projects. The selection process includes preliminary selection based on capacities and costs, followed by an assessment by an external auditor and a member of EVI. The selection of a sponsor is based on the assessment results and is further recommended by the EVI SAC and approved by the EVI Board.

AMA1-DiCo

The AMA1-DiCo phase Ia/Ib clinical trial will be staggered, randomised, double-blind, multi-centre trial in healthy malaria non-exposed European adults and malaria exposed African adults.

The clinical trial will evaluate the safety and immunogenicity of a 50-µg dose of the AMA1-DiCo malaria vaccine candidate with GLA-SE and aluminium hydroxide as the adjuvant, in healthy European adults not previously exposed to the parasite *P. falciparum* and in healthy African adults previously exposed to the parasite. The safety of the vaccine in European subjects will be evaluated by an independent DSMB before transition of the clinical trial to previously exposed African subjects.

The sponsor of the clinical trial is Inserm, France. Prof. Odile Launay (CIC Cochin, Paris, France) will conduct the clinical trial arm in the non-exposed population, and Dr Sodiomon Sirima (CNRFP, Ougadougou, Burkina Faso) will conduct the clinical trial arm in the exposed population.

Once the protocol was approved by the COSSEC of Inserm in March, the sponsor delivered a pre-submission of the clinical trial dossier to the French regulatory agency, ANSM. The sponsor submitted the dossier to the French local ethics committee (CPP) in May. Following a positive CPP opinion, the CTA was submitted to ANSM in September. Authorisation to proceed with the clinical trial in France was received in November. After authorisation to proceed with the clinical trial in France, the dossier was submitted to national and local ethics committees in Burkina Faso in November. A positive opinion was received in December from both ethics committees.

The first immunisation in the phase Ia/Ib AMA1-DiCo clinical trial was scheduled to take place in France in January 2014.

P27A

The P27A phase Ia/Ib clinical trial will be staggered, randomised, single-blind, antigen and adjuvant dose-finding, multi-centre trial in healthy malaria non-exposed European adults and malaria exposed African adults.

The clinical trial will evaluate the safety and immunogenicity of the P27A malaria vaccine candidate with GLA-SE and aluminium hydroxide as the adjuvant, in healthy European adults not previously exposed to *P. falciparum* and in healthy African adults previously exposed to the parasite. The safety of the vaccine in European subjects will be evaluated

by an independent DSMB before transition of the clinical trial to previously exposed African subjects.

The sponsor of the clinical trial is CHUV, Switzerland. Prof. François Spertini (CHUV, Switzerland) will conduct the evaluation of the vaccine in the non-exposed population, and Dr Seif Shekalaghe (IHI, Bagamoyo, Tanzania) will conduct the clinical trial arm in the exposed population.

The principal investigator at CHUV submitted the dossier to the Swiss local ethics committee (CCEV) in May. Following their positive opinion in July, the sponsor submitted the CTA to the Swiss regulatory agency, Swissmedic. Authorisation to proceed with the clinical trial in Switzerland was received in November. The CTA supported with the document acknowledging the positive opinion of the Swiss local ethics committee was submitted to the IHI-IRB and to the Tanzania Food and Drugs Authority in July. Ethical clearance to conduct the study in Bagamoyo was received in December.

The first immunisation in the phase Ia/Ib P27A clinical trial was scheduled to take place in Switzerland in first quarter of 2014.

PRIMALVAC

The PRIMALVAC project is expected to carry out a phase Ia/Ib clinical trial in healthy adult subjects not previously exposed to malaria and in exposed subjects in malaria-endemic regions in sub-Saharan Africa. The clinical trial will be designed to assess the safety and immunogenicity of different dosages of the var2CSA DBL1-2 vaccine candidate in aluminium hydroxide and a second adjuvant that has yet to be defined. Sponsorship is currently under negotiation.

PlacMalVac

The first phase Ia/Ib clinical trial will be designed to assess the safety and immunogenicity of different dosages of the selected var2CSA vaccine candidate in healthy adult subjects not previously exposed to malaria and in exposed subjects in malaria-endemic regions in sub-Saharan Africa. The sponsor, assessed by EVI in July, will be EKUT. The coordinating principal investigator will be Prof. Peter Kremsner, EKUT. In December, EVI conducted a site assessment to address the feasibility of a phase Ib clinical trial and to provide support to the CERPAGE, Université d'Abomey-Calavi, Benin. The clinical trial is expected to start by the end of 2015.

CSVAC

The phase Ia clinical trial was an open, non-randomised trial to assess the safety and immunogenicity of ChAd63 and MVA replication-deficient viral vectored vaccines, both encoding the *P. falciparum* CSP, in healthy adult subjects not previously exposed to malaria. Two different doses (5×10^9 and 5×10^{10} VPs) of ChAd63 followed by 2×10^8 plaque forming units of MVA CSP were administered intramuscularly in a heterologous prime-boost regimen eight weeks apart.

The clinical trial was sponsored by UOXF and conducted at the Clinical Research Centre RCSI (Prof. Sam McConkey). The clinical trial was completed by the end of 2012, and sample analysis and report writing were completed during 2013. The project officially closed on 31 July 2013 after a no-cost extension during 2012.

The vaccine combination was found to be safe and well tolerated at both doses. The reported adverse events were of the nature and severity described in the investigator brochure and no serious adverse events were observed. All vaccinations, subject visits and

ELISpot assays were carried out according to protocol. The ELISpot assay results showed that both doses of ChAd63 CSP were immunogenic, inducing high-level T-cell responses. Regarding the breadth of the CSP response, T-cell responses in all subjects were detected in multiple peptide pools spanning the entire CSP vaccine insert in the ex vivo IFN-□ ELISpot assay. Following the priming immunisation with ChAd63 CSP, individual responses were seen across all pools with no apparent single immunodominant region.

MVVC

The MVVC project intends to conduct a series of clinical trials to determine whether a prime-boost vaccine combination using ChAd63 ME-TRAP and MVA ME-TRAP is safe and immunogenic and will lead to efficacy in the target population.

A phase Ib clinical trial of these vaccine candidates was carried out at MRC Gambia in adults and in infants aged 5–12 months and 10 weeks. The vaccine candidates achieved a good safety profile and good immunogenicity data were obtained. No SAEs related to the vaccine candidates were reported. The results of the phase Ib adult clinical trials have been published in PLoS One[17]. Manuscripts are in preparation for the adult phase Ib clinical trial immunology data and the phase Ib clinical trial in children and infants.

A phase IIb adult efficacy trial has been completed at KEMRI and UCAD. The KEMRI phase IIb efficacy data are promising and have been submitted for publication. The UCAD phase IIb clinical trial data are now being analysed.

A phase Ib lead-in/IIb clinical trial in the target age group (5–17 month old infants and children) commenced in the fourth quarter of 2012 at CNRFP. The last of the 700 subjects was enrolled in August 2013, and the follow-up is underway. The first results are expected in the first half of 2014.

The recruitment and follow-up of subjects enrolled in the baseline epidemiological studies at UCAD and CNRFP in the fourth quarter of 2011 continued during the year and follow-up was completed in 2013. All recruitment targets have been met at both sites. Data analysis is now underway.

MVVC 2

This project aims to determine whether malaria-vectored prime-boost vaccines are compatible with the EPI vaccination schedule and whether the addition of a CSP particle in the adjuvant will enhance the efficacy of vectored prime-boost vaccines.

The safety and immunogenicity of the vectored liver-stage malaria vaccine candidates co-administered with EPI vaccines will be assessed in Gambian infants at the MRC in a collaborative clinical trial with the support of the UCAD team. The safety, immunogenicity and efficacy of the CSP particle in adjuvant alone and combined with the vectored malaria vaccine candidates will be assessed in African adults at the CNRFP in Burkina Faso. Both clinical trials will begin in 2014.

SPOROVAC

The objective of the project is to complete a clinical trial in Africa to assess safety and efficacy of vaccination with life-attenuated whole *P. falciparum* sporozoites under a chemo-

[17] Ogwang C. et al. (2013). Safety and immunogenicity of heterologous prime-boost immunisation with *Plasmodium falciparum* malaria candidate vaccines, ChAd63 ME-TRAP and MVA METRAP, in healthy Gambian and Kenyan adults. PLOS One, 8(3). doi: 10.1371/journal.pone.0057726.

prophylaxis regime following a controlled human malaria challenge using a heterologous strain. The sponsor of the clinical trial is Sanaria Inc. and the clinical trial will be conducted at the IHI, Tanzania, by Dr Salim Abdulla.

The US FDA requested that the heterologous 7G8 strain should also be assessed in biodistribution tests and dose-finding studies. Sanaria handed an amendment to EVI in February, requesting a change in the clinical trial design, in which the heterologous challenge with the *P. falciparum* strain 7G8 is replaced by a homologous challenge with the NF54 strain also used for the initial immunisations. Sanaria plans to reinstate the heterologous challenge as soon as funding has been identified and the studies requested by the US FDA have been completed.

Furthermore, a study similar to the SPOROVAC clinical trial was scheduled to be carried out at EKUT, Germany. After Sanaria's request for an amendment, EVI made the approval of the EKUT CTP by the German regulatory agency PEI a prerequisite for the continuation of the SPOROVAC project. Delays in the submission of the CTP to the PEI therefore also led to delays in the SPOROVAC clinical trial in Tanzania. The start of the clinical trial was therefore postponed to the first quarter of 2014.

In March, a pre-IND meeting with the Tanzanian FDA resulted in the broad approval of the clinical trial design with only minor comments. Additionally, an ICH-GCP audit of Sanaria for sponsorship was completed in April.

MultiMalVax

The aim of the MultiMalVax project is to develop the concept of a highly-effective multi-stage malaria vaccine to the point of proof-of-concept phase II efficacy testing in Europe, prior to clinical trials in malaria-endemic areas. The overarching aim of this four year clinical development programme is to show safety, immunogenicity and efficacy at each stage of the parasite life cycle using a multi-stage malaria vaccine, which could provide a deployable high-efficacy product for use in malaria-endemic areas.

The blood-stage malaria vaccine trial using the Rh5 antigen delivered by viral vectors is expected to start at UOXF in the second quarter of 2014. The pre-erythrocytic vaccine trial using the RTS,S biosimilar R21, and the transmission-blocking vaccine trial, are expected to start by the end of 2014 or early 2015. The investigational site for the transmission-blocking vaccine trial has yet to be selected. A call was launched on 6 September 2013. The delay in the production of the vaccine candidate has postponed the selection of the investigational centre until later in 2014. Therefore, the call will be re-launched to ensure a fair selection process with accurate timelines for the implementation of the clinical trial.

PIM

The PIM project aims to develop the first controlled human challenge model of paratyphoid infection that can be used to investigate the pathogenesis and immunobiology of infection, identify biomarkers and evaluate the efficacy of vaccine candidates.

To determine the dose of *Salmonella paratyphi A* required for the development of the human challenge model, healthy volunteers will be challenged with escalating doses of *Salmonella paratyphi A* until the clinical or laboratory attack rate reaches 55–75%. Immunological and transcriptomic analysis will be undertaken to characterise the immune response and identify factors associated with resistance to infection. Regulatory approval will be sought from the Oxfordshire NHS REC, and the challenge study is scheduled to begin later in 2014.

BELLEROPHON

The clinical trial of the *Staphylococcus aureus* vaccine candidates evaluated during this project will begin during fourth quarter of 2015. The clinical trial will take place in the UK with healthy adult subjects 18–50 years of age.

IDEA

The IDEA work package that measures the impact of intestinal helminth infections on the immune response to TB, malaria and HIV vaccines is led jointly by UOXF and EVI, and their activities commenced in April 2011.

The add-on studies for malaria vaccine trials (GMZ2) in Lambaréné, Gabon, were completed by the beginning of 2013. Samples have been collected in order to analyse the influence of helminth infection on vaccine-induced immunity. The immunological results should be available in mid-2014.

Due to the low prevalence of worm infections at the selected HIV and TB vaccine investigational sites at the time the proposal was written, it was decided in September 2012 to conduct two small stand-alone phase I clinical trials. The UVRI was selected as the site for both clinical trials in May. The TB study will test the effect of *Schistosoma mansoni* infections on the immunogenicity of the MVA 85A TB vaccine candidate in African adolescents vaccinated with BCG. The HIV study will evaluate the safety and immunogenicity of candidate HIV vaccines, including a DNA prime followed by a NYVAC boost in HIV-1-free adult participants with or without underlying schistosomiasis infections. The CTP is now under review by the UVRI SEC. The clinical trial should start during the first half of 2014.

CAPACITY BUILDING, WORKSHOPS, TRAINING

Capacity Building

P27A

The building permit for the outpatient wing intended for the P27A clinical trial at BCTU, Tanzania, has been secured. The cost of the outpatient wing is partly supported by the EDCTP P27A-CTB strategic primer grant.

MVVC

The site infrastructure and laboratory equipment upgrade has been completed at the CNRFP site in Banfora, Burkina Faso, and at the UCAD research site in Keur Socé, Senegal. Both sites are now functioning effectively.

Several exchange visits took place during this reporting period to reinforce collaboration especially among the African project partners.

MVVC 2

As above, exchange visits took place during this reporting period to reinforce collaboration especially among the African project partners.

IDEA

The following technologies were transferred between the IDEA partners: malaria PCR, stool PCR (in Uganda and Mbeya, Tanzania), and Luminex. Human capacity building also increased, with special emphasis on immunology in Africa. Multiple North-South and South-South exchanges have taken place.

Workshops

PlacMalVac

A round table entitled "*The challenge of developing a PAM vaccine*" was organised by EVI as part of the MIM Pan-African Malaria Conference in Durban, South Africa, with Alister Craig as the chair (Liverpool School of Tropical Medicine, Liverpool, United Kingdom) and Odile Leroy as vice-chair. Experts on PAM discussed the relevance of developing a PAM vaccine, the challenges encountered, as well as the development of preferred product characteristics and the clinical development plan of a PAM vaccine.

MVVC

A publication-writing workshop was organised by EVI with assistance from CNRFP in Ouagadougou, Burkina Faso, on 27–30 August. This workshop was presented by Dr Barbara Janssens and Dr Maria Mavris and was attended by 13 participants from the four MVVC African partner sites. The participants attended four days of lectures, discussions focusing on topics such as article structure and figure design, and practical exercises.

EDUFLUVAC

A workshop on IP rights and technology transfer management was organised for the consortium partners by Christian Mittelholzer, Redbiotec AG, Switzerland, during the EDUFLUVAC kick-off meeting in Heidelberg, Germany on 20 November. The aim of this workshop was to outline strategies to guarantee IP protection of the research results and ensure that knowledge generated during the project could be readily exploited through selected licensing opportunities.

TRANSVAC

Workshop on global analysis platforms for HIV, TB and malaria

This workshop was held on 6 March at the IWH in Heidelberg, Germany. It was organised with the help of the TBVI, the Netherlands, and was chaired by Stefan Kaufmann, MPIIB, Germany. The objectives of the workshop were to bring together experts in the HIV, malaria and TB fields to exchange views and find ways forward on the standardisation and harmonisation of global analysis platforms to monitor host responses in preclinical and clinical vaccine development, and the comparison of datasets between different global analysis platforms and with datasets obtained using other technologies. These ideas were discussed with the aim to accelerate the development of markers and biosignatures of immunity or efficacy for use in the preclinical and clinical development of vaccines.

The workshop concluded that only a few 'global analysis' platforms are fully standardised to the extent that they can be used informatively in preclinical studies and clinical trials through which licensure could be obtained. Coordinated efforts among the different disease networks should therefore continue to strive for the standardisation of immunological and global platforms to ensure their effective use in clinical settings, their use for biomarker discovery and validation, and their use in the generation of datasets that can be compared between platforms and across different preclinical settings and/or different clinical trials. The main challenges to be overcome in the context of global analysis can be grouped into the following areas:

1. Definition of study group sizes and numbers in order to compare studies.
2. Recommendations for sample collection and storage for future analysis, wherever possible according to generally accepted recommendations.

3. Understanding the environmental influence on host responses. Not all variables can be taken into account during clinical trials and it is important to identify parameters with the greatest influence and harmonise the methods used to monitor them.
4. Establishment of internal standards and controls to ensure the comparability, efficiency and feasibility of molecular and immunological profiling.
5. A manuscript summarising the conclusions of the workshop has been submitted to the journal *Vaccine*.

Animal model workshops

The animal model workshops were organised by the CVI and BPRC, the Netherlands, with the help of EVI and TBVI. A third workshop entitled "*The asterisk, who cares? Data analysis of animal studies with multi-variables and small numbers of animals*" took place on 6 June in Amsterdam, the Netherlands, and was attended by 12 participants. The objective of the workshop was highly appreciated and the need for information about analysis methods for studies with small groups of animals was emphasised. The intention of the workshop was to bring together animal researchers and statisticians and bridge the gap between them.

A fourth workshop entitled "*The pig as a model in human vaccine development*" took place on 20 September at CVI in Lelystad, the Netherlands, and was attended by 55 participants. The objective of the workshop and the resulting information were highly appreciated. The dual purpose was to inform both the vaccine developers and animal modellers about recent developments and the possibilities and limits of the pig as a model species. The chairman concluded that the contributions from diverse scientific fields enhanceed the quality of the meeting and that such a multidisciplinary approach helped to complete the picture. A publication covering the content of the presentations and discussions in the workshop is in preparation.

Vaccine development stakeholders' workshop

In collaboration with European vaccine stakeholders, the TRANSVAC consortium prepared a roadmap which aimed to secure sustainable vaccine development infrastructures in Europe. Using a bottom-up approach, the needs and priorities of European vaccine R&D were identified through a series of stakeholder consultations and workshops, and translated into a proposal to establish an EVRI.

The advanced draft of a roadmap was presented and discussed at the TRANSVAC annual meeting in March, and then circulated for comments and validation among the European stakeholders. Overall, the feedback received from the consultation process was very positive. In addition, a detailed questionnaire included in the first round of consultation confirmed the high priority of the proposed activities and services, as perceived by European vaccine stakeholders.

Finally, the proposal for a European vaccine R&D infrastructure was discussed and validated during a workshop held at the Royal Flemish Academy of Belgium for Science and the Arts in Brussels, Belgium, on 20 June. The workshop was attended by 70 representatives of vaccine developers and manufacturers (academic researchers, biotechnology companies, large vaccine development companies, PDPs and other European vaccine-related projects), regulatory authorities, international and national policy makers, and funding agencies. European vaccine stakeholders at the workshop supported the establishment of an EVRI as presented in the roadmap, and many of them expressed their intention to join the initiative. It was acknowledged that the EVRI addresses several needs of European vaccine developers, has the potential to accelerate the development of

new and improved vaccines, and shares the vision of the European research agenda Horizon 2020.

The roadmap has been finalised and is now available on the TRANSVAC website. Paper versions of the roadmap will be sent to relevant governmental bodies.

In order to continue its activities and to put in place the EVRI, TRANSVAC will apply to the EC Horizon 2020 call on European research infrastructures.

Training

P27A

In March, a two-day training course on GCP and GCLP was organised by EVI at the IHI BCTU, Tanzania. The course was presented by Rita Walt (accredited by Swissmedic) and supported by the EDCTP P27A-CTB strategic primer grant. The topics in the course included an introduction to the principles of GCP and GCLP, ethics in clinical research, the role of the investigational staff and the sponsor, safety reporting, clinical trials data management, organisation and management of a GCLP-compliant laboratory, an introduction of quality systems, audits and inspections.

Kassim Kamaka, clinical trial coordinator at IHI, was trained in October on clinical trial coordination at Swiss TPH in Basel.

Catherine Mkindi was selected in March and registered as a PhD student in September at the University of Basel. Her research work focuses on the analysis of immune responses induced by the malaria peptide P27A following administration to Tanzanian subjects with either alhydrogel or GLA-SE. The PhD fellowship is supported by the EDCTP P27A-CTB grant.

Maxmillian Mpina, who started his PhD work on harmonisation and immunoassay development for the P27A clinical trial at IHI and at the CHUV in 2012, continued his research during 2013.

MVVC

Ya Jankey Jagne from the MRC in the Gambia successfully completed her studies at the LSHTM and graduated with a Master's degree in Immunology of Infectious Diseases in November. Francis Ndungu from the KEMRI finished his postdoctoral training supported by MVVC in December with several immunological studies published in international journals (see *Publications*). The other four post-graduates (three PhD students and one Master's student at the African sites) are still undergoing training.

MVVC 2

A statistician from the KHRC received statistical training in July at the LSHTM ("*Introduction to infectious disease modelling and its applications*"). A second KHRC employee started training in September on "*Statistical methods*" at Hasselt University in Belgium.

SPOROVAC

In March, the SPOROVAC clinical trial team benefited from a two-day training course on GCP and GCLP that was organised by the EVI at the IHI BCTU in Bagamoyo, Tanzania, and funded by EDCTP under the P27A-CTB strategic primer grant. Two EVI members involved in SPOROVAC attended the training. The course enhanced networking and collaboration between the EVI team and the Bagamoyo team involved in the SPOROVAC clinical trial.

IDEA

In 2013, the IDEA project brought the total number of fellowships to eight Master's students at UVRI, Uganda, Lambaréné, Gabon and Bagamoyo, Tanzania, and 16 PhD students at UVRI, IHI, Tanzania, Mbeya, Tanzania, Lambaréné, Gabon, University of Ibadan, Nigeria and KEMRI, Kenya.

An additional two-week short course in immunology was organised at MRC UVRI, Uganda, in March and September and was attended by participants from the IDEA and Schistovac projects. The course provided added value by promoting collaborations.

TRANSVAC

In March, the second four-day training course "*Practical approaches to vaccine development*" was organised and held at the VFL, UNIL, Switzerland, and 15 participants working in vaccine development were selected through a competitive process. The course registration fees and hotel accommodation costs were covered by the TRANSVAC project. Overall, 28 experts from industry, academia, government institutions, public bodies and consultants presented numerous aspects of vaccine development, providing a thorough overview of the full vaccine development process. The number of applications received for the two courses and the resulting positive feedback highlight the success of the two TRANSVAC training courses and emphasise the demand for such courses within the European vaccine community.

Sagida Bibi, Aston University, Birmingham, UK, published her thesis entitled "*The formulation of artificial reference standards for use within the ELISpot assay*" in June.

HARMONISATION

MVVC

The antibody and T-cell assays are well standardised between consortium centres. The antibody assays, conducted for the baseline studies, were centralised in KEMRI and data were normalised by the use of standard controls with known antibody concentrations in each plate. The T-cell assays use an identical protocol, with identical operating procedures, an achievement that has been made possible by a series of exchange trips and collaboration with a quality control network. Reagents for ELISpot assays were purchased from agreed suppliers and were standardised between centres. In addition, the sites involved in the immunogenicity studies are part of the OPTIMALVAC network to process shared samples, and an agreement was reached among the sites for specific responses and controls.

MVVC 2

The MVVC 2 consortium is expanding the MVVC harmonisation efforts on immunoassays to KHRC and those on qPCR to CNRFP. This will ensure that the sites achieve comparable results in the MVVC 2 project and in future clinical trials.

SPOROVAC

Exposing healthy human volunteers to *P. falciparum*-infected mosquitoes (so-called CHMI) is an accepted tool to evaluate the preliminary efficacy of malaria vaccines. During the planned SPOROVAC clinical trial, volunteers will undergo CHMI with live, fully-infective sporozoites under chemoprophylaxis. Challenges to evaluate the protective effect of this approach will also be conducted by the injection of fully-infective sporozoites. A qPCR assay will be used to detect any *P. falciparum* parasites in blood samples from the volunteers.

As part of the ongoing optimisation of the CHMI model, there is a general consensus among CHMI centres that the qPCR results for parasite load need to be comparable, especially because more groups and centres (e.g. in Africa and India) are currently setting up CHMI infrastructure.

The SPOROVAC project is therefore attempting to harmonise the qPCR assay in the CHMI institutions. Meetings with representatives from these institutions and other interest groups took place in April in Lausanne, Switzerland, during the MVW symposium, and in November at the ASTMH conference in Washington DC, USA. The results of preliminary harmonisation efforts (e.g. pilot production of common standards) were presented by Sean Murphy during the EVI Rendez-Vous on 4 December.

PIM

The development of a controlled human model of paratyphoid infection is necessary to accelerate the development of paratyphoid vaccines. This model will allow the rapid evaluation of vaccine efficacy, by providing early proof of the vaccine concept, to directly compare clinical features, laboratory parameters and biomarkers, and to identify potential correlates of protection.

IDEA

Significant efforts have been made towards the harmonisation of immunological assays and diagnostic methods across the study sites, e.g. the harmonisation of SOPs for the isolation and stimulation of dendritic cells, monocytes and B cells, $CD4^+$ and $CD8^+$ T cells, PBMC isolation and cryopreservation, ELISpot assays, functional polychromatic flow cytometry and Luminex technology. Criteria for the acquisition of infection, disease progression and response to therapy were also harmonised, in addition to protocols for worms and HIV, TB and malaria among the different study sites.

TRANSVAC

Harmonisation of immunoassays for clinical trials

The TRANSVAC project focussed on the establishment of assays and protocol transfer, followed by assay harmonisation in terms of performance and reproducibility within and between groups. The harmonisation of three assays for vaccine-induced T-cell responses has been optimised, finalised and agreed by the three participating laboratories: an ELISpot assay, an ICS assay and an ELISA, each designed to measure antigen-specific INF-□ expression. Key operational specifications were also identified. Regulatory considerations have been taken into account during the harmonisation process and the data showed robust reproducibility within the specialist laboratories and between operators. The harmonised assay SOPs were published on the TRANSVAC website and made freely available to the scientific community.

Harmonisation of the global analysis platform

Inter-platform comparison and harmonisation of Agilent microarrays (MPIIB), Affymetrix microarrays (LIONEX) and Illumina deep sequencing (HZI) technologies was performed using BCG clinical trial samples. Harmonisation of SOPs for sample analysis, microarray analysis and data analysis was achieved across the three platforms. The aim of the comparison was not only to compare the performance of the different technologies, but also to standardise the different overall correlation approaches, such as up-down classification, correlation coefficients and tables of contingency with other immunoassay technologies such as ICS, ELISpot and cytokine/chemokine expression patterns. The partners analysed 77, 74 and 32 human RNA samples isolated from blood samples taken

during a phase Ia clinical trial of *M. bovis* BCG vaccination, using the Affymetrix, Agilent and Illumina platforms, respectively. The Affymetrix platform and Partek Software package provided the most reliable and thorough analysis, which was ideal for the identification of relevant biomarkers. These data must now be analysed together with in vitro assays and protection data.

OUTREACH, COMMUNICATION

AMA1-DiCo

Pierre Loulergue (Groupe Hospitalier Cochin Broca Hôtel Dieu (CIC, BT505), Paris, France) presented "*AMA1-DiCo CT phase Ia/Ib challenges and status*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

InnoMalVac

Annie Mo (NIH, Bethesda, USA), Ashley Birkett (MVI, Washington DC, USA), and Simon Draper (The Jenner Institute, Oxford, UK) presented "*Rh5 – an update on the different vaccine developments*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

P27A

François Spertini (CHUV, Lausanne, Switzerland) presented:

- "*Two blood-stage candidate vaccines: PfPEBS and P27A: an update*" at the MVW Conference on 22–24 April, Lausanne, Switzerland
- "*P27A staggered phase Ia/Ib CT: an update*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

PRIMALVAC

Arnaud Chêne (Inserm, Paris, France) reported PRIMALVAC progress at the EVI 15th Anniversary Symposium, 26 February, Heidelberg, Germany.

Nicola Viebig (EVI, Heidelberg, Germany) presented "'*PRIMALVAC: var2CSA as a pregnancy-associated malaria vaccine candidate*" at the MVW Conference, 22–24 April, Lausanne, Switzerland.

Benoit Gamain (Inserm, Paris, France) reported on-going PRIMALVAC work at:

- The 6th MIM Pan-African Malaria Conference, 6-11 October, Durban, South Africa as part of the round table symposium (see below)
- The 62nd ASTMH, 13–17 November, Washington DC, USA
- The EVI Rendez-Vous, 4 December, Heidelberg, Germany.

A round table entitled "*The challenge of developing a pregnancy-associated malaria vaccine*" was organised by EVI as part of the 6th MIM Pan-African Malaria Conference in Durban, South Africa, with Alister Craig as the chair (Liverpool School of Tropical Medicine, Liverpool, United Kingdom) and Odile Leroy as vice-chair (EVI, Heidelberg, Germany). PAM experts discussed the relevance of developing a PAM vaccine, the challenges encountered, as well as the development of preferred product characteristics and the clinical development plan for the PAM vaccine.

A press release presenting the three EVI PAM projects was distributed in February by Market Wire.

PAMCPH

Ali Salanti (UCPH, Denmark) presented:

- "*Development of a var2CSA-based placental malaria vaccine*" at the 8th European Congress on Tropical Medicine and International Health, 10–13 September, Copenhagen, Denmark.
- "*Defining the antigen for a var2CSA-based vaccine*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany

Wian de Jongh (ExpreS2ion Biotechnologies, Copenhagen, Denmark) reported the production phase of the project at:

- The 6th Annual Cell Culture Technology Event on 7 March in London, UK
- New Cells New Vaccines, 17–20 March, Wilmington, USA
- The PEGS, 29 April to 3 May, Boston, USA
- The "Continuous Bioprocesses" workshop, 1-2 July. Cambridge, UK
- The "Single Use" workshop, 8 October, Shanghai, China
- The PEGS Europe, 4–7 November, Lisbon, Portugal

Charlotte Dyring (ExpreS2ion Biotechnologies, Copenhagen, Denmark) presented the PAMCPH project at:

- The European Society for Animal Cell Technology meeting, 23-27 June, Lille, France
- The Biomed meeting, 10-12 June, Tel Aviv, Israel
- The Nordic Life Sciences Days, 14-15 October, Stockholm, Sweden.

A round table entitled "*The challenge of developing a pregnancy-associated malaria vaccine*" was organised by EVI as part of the 6th MIM Pan-African Malaria Conference in Durban, South Africa, with Alister Craig as the chair (Liverpool School of Tropical Medicine, Liverpool, United Kingdom) and Odile Leroy as vice-chair (EVI, Heidelberg, Germany). PAM experts discussed progress towards a PAM vaccine, the challenges encountered, the development of preferred product characteristics and the clinical development plan for the PAM vaccine.

A press release presenting the three EVI PAM projects was distributed in February by Market Wire.

PlacMalVac

The PlacMalVac kick-off meeting was held on 25 April in Copenhagen, Denmark, where the consortium members presented their work in each work package.

Saadou Issifou, Université d'Abomey-Calavi, Cotonou, Bénin, presented "*Overview of the clinical development plan of a var2CSA-based pregnancy associated malaria vaccine*" at the 6th MIM Pan-African Malaria Conference on 6–11 October, Durban, South Africa.

A round table entitled "*The challenge of developing a pregnancy-associated malaria vaccine*" was organised by EVI as part of the 6th MIM Pan-African Malaria Conference in Durban, South Africa, with Alister Craig as the chair (Liverpool School of Tropical Medicine, Liverpool, United Kingdom) and Odile Leroy as vice-chair (EVI, Heidelberg, Germany). PAM experts discussed progress towards a PAM vaccine, the challenges encountered, the development of preferred product characteristics and the clinical development plan for the PAM vaccine.

A press release presenting the three EVI PAM projects was distributed in February by Market Wire.

CSVAC

Eoghan de Barra, RSCI, Dublin, Ireland, presented "*A phase Ia study to assess the safety and immunogenicity of new malaria vaccine candidates ChAd63 CS administered alone and with MVA CS*" at the MVW Conference, 22–24 April, Lausanne, Switzerland, as well as "*Safety and immunogenicity of new malaria vaccine candidate ChAd63 CS administered alone and with MVA CS*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

MVVC

The MVVC Annual Meeting took place on 14–17 January in Dakar, Senegal. The partners presented updates on recent results and activities in the different work packages and the next steps were discussed.

Egeruan Babatunde Imoukhuede, EVI, Heidelberg, Germany, presented "*The Malaria Vectored Vaccines Consortium (MVVC)*" at the MVW conference, 22–24 April, Lausanne, Switzerland.

Nicola Viebig, EVI, Heidelberg, Germany, presented "*The MVVC: Integrating capacity building and networking in the design and conduct of CTs in East and West Africa*" at the 6th MIM PAN African Malaria Conference, 6–11 October, Durban, South Africa.

Adrian Hill, UOXF, Oxford, UK, and Caroline Ogwang, KEMRI, Kilifi, Kenya, organised the "*Symposium on multi-stage multi-component malaria vaccines*" at the 6th MIM PAN African Malaria Conference, 6–11 October, Durban, South Africa.

Caroline Ogwang, KEMRI, Kilifi, Kenya, presented the KEMRI phase IIb clinical trial results at the 62nd ASTMH meeting, 13–17 November, Washington DC, USA.

Caroline Ogwang, KEMRI, Kilifi, Kenya and Victorine Mensah, Université Cheikh Anta Diop, Dakar, Senegal, presented "*Safety, immunogenicity and efficacy of ChAd63 ME-TRAP boosted with MVA ME-TRAP in Kenya and Senegal*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

Alfred Tiono, CNRFP, Ouagadougou, Burkina Faso, presented "*How capacity building has allowed a phase II efficacy trial in Burkina Faso*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

SPOROVAC

A face-to-face meeting was organised by EVI in April in Lausanne, Switzerland, during the MVW Symposium, with the aim of harmonising the qPCR assays among the institutions conducting CHMI studies and thus improving the comparability of qPCR results. These harmonisation efforts were reviewed at a side meeting in Washington in November during the 62nd ASTMH meeting.

Stephen Hoffman, Sanaria Inc., Rockville, USA, presented "*SPOROVAC: Update and the regulatory road towards starting the first CHMI trial in Africa*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

Sean Murphy, University of Washington, Seattle, USA, presented "*Towards harmonised molecular diagnostics in the controlled human malaria infection model*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

MultiMalVax

Adrian Hill, The Jenner Institute, UOXF, Oxford, UK, organised the "*Symposium on multi-stage multi-component malaria vaccines*" at the 6th MIM PAN African Malaria Conference, 6–11 October in Durban, South Africa.

Adrian Hill, The Jenner Institute, Oxford, UK, presented "*Challenge of developing a multi-component multistage malaria vaccine*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

The MultiMalVax annual meeting took place on 7–8 November in Heidelberg, Germany. The partners presented updates on recent results and activities in the different work packages and the next steps were discussed.

PIM

Andrew Pollard, UOXF, Oxford, UK, presented "*Paratyphoid human infection model*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

BELLEROPHON

A press release was published by Imaxio, Lyon, France, in July, prior to the start of the BELLEROPHON project, in order to disseminate the successful application for EC funding for the development of a *Staphylococcus aureus* vaccine.

The BELLEROPHON kick-off meeting took place on 12–13 September in Oxford, UK, where the partners discussed the scientific and organisational aspects of the project. The newly selected ISAC members provided positive feedback and the EC officers offered guidance for the management of the project.

Fergal Hill, Imaxio, Lyon, France, presented "*Combining cellular and humoral immune responses as a vaccine strategy against S. aureus pathogen*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

EDUFLUVAC

The EDUFLUVAC kick-off meeting was held in Heidelberg, Germany, on 20 November. The partners enthusiastically presented the work to be carried out in their institutions. Excellent communication between the partners, which is crucial for this project, was already evident in the meeting.

Ed Remarque (BPRC, Rijswijk, The Netherlands) presented "*EDUFLUVAC: Universal flu vaccine based of diversity covering approach*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

IDEA

The IDEA annual meeting was held on 25–27 September in Dar es Salaam, Tanzania. The meeting discussed project updates and future activities. The annual meeting also incorporated visits to the Mbeya and Bagamoyo investigational sites.

Benjamin Mordmüller, EKUT, Tübingen, Germany, presented "*Helminths and malaria*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

TRANSVAC

The final TRANSVAC annual meeting was held on 7–8 March in Heidelberg, Germany. The partners were enthusiastic about the reported progress and set up timelines to finalise all the work before the end of the project. Lessons learnt from the project were also discussed in the context of continuing the project via the EC Horizon 2020 call.

Frank Verreck, BPRC, Rijswijk, The Netherlands, presented "*Overview of major findings of the WP12 TNA NHP Study with SSI"* at the NEWTBVAC Annual Meeting (FP7 Consortium) on 29 January to 1 February, Les Diablerets, Switzerland.

Nicolas Collin, UNIL, Lausanne, Switzerland, presented "*The Vaccine Formulation Laboratory: a platform to facilitate access to vaccine adjuvants and formulation services*" at the EVI 15th Anniversary Symposium, 26 February, Heidelberg, Germany.

Odile Leroy, EVI, Heidelberg, Germany, presented "*Developments in vaccines for infectious disease"* at the symposium "Emerging and re-emerging infectious diseases: how prepared are we for the global threat?", 2 March, Munich, Germany.

Steven Smith, LSHTM, London, UK, presented "*Cytokine expression profile of Mycobacterium tuberculosis PPD-specific CD4$^+$ T-cells that are detectable 3 and 12 months following BCG vaccination of UK infants*" at the TB Vaccines Global Forum, 24 March, Cape Town, South Africa.

Patrick Dubois, UNIL, Lausanne, Switzerland, presented "*Formulation development at the Vaccine Formulation Laboratory*" at the Canadian Adjuvant Workshop, 26 March, Ottawa, Canada.

Mark Geels, EVI, Heidelberg, Germany, presented "*TRANSVAC, European network of vaccine research and development*" at the 3rd MVW Conference, 22–24 April, Lausanne, Switzerland.

Nicolas Collin, UNIL, Lausanne, Switzerland, presented "*Addressing the challenge of access to adjuvants*" at the Modern Vaccine Adjuvants Formulation meeting, 15–17 May, Lausanne, Switzerland.

Frank Verreck, BPRC, Rijswijk, the Netherlands, presented "*Overview of major findings of the WP12 TNA NHP Study with SSI*" at the 9th Elsinore Meeting in Infection Immunity on "Translating Breakthroughs in Immunology into Vaccines of Global Importance", 29–31 May, Helsingør, Denmark.

Christophe Barnier-Quer, UNIL, Lausanne, Switzerland, presented "*Basic and clinical research on administration routes of vaccines*" at the Corevac Meeting on 30 May at Institut Pasteur, Paris, France.

Hazel Dockrell, LSHTM, London, UK, presented "*What would make a good biomarker for susceptibility of protection against TB?*" at the "TB or not TB" conference, 19 September, Borstel, Germany.

Sebastian Weißman, HZI, Braunschweig, Germany presented "*Novel candidate adjuvants for tailoring immune responses*", 25–27 September, Copenhagen, Denmark.

Frank Verreck, BPRC, Rijswijk, the Netherlands, presented "*Overview of the rhesus spectrotype comparison NHP in vivo study results on TB disease susceptibility and BCG protective efficacy*" at the AERAS Workshop on "NHP TB Model Development", 3 October, Rockville, USA.

Odile Leroy, EVI, Heidelberg, Germany, presented "*A world free of the intolerable burden of diseases of poverty*" at the 14th World Vaccine Congress on 16–17 October in Lille, France.

Céline Dutruel, EVI, Heidelberg, Germany, presented "*TRANSVAC, European network of vaccine research and development*" at the 7th Vaccine and International Society for Vaccines Congress, 27–29 October, Sitges, Barcelona, Spain.

Odile Leroy, EVI, Heidelberg, Germany, presented "*Learning from TRANSVAC: The Vaccine R&D Infrastructure Roadmap*" at the EVI Rendez-Vous, 4 December, Heidelberg, Germany.

IPROVE

The kick-off meeting of the project took place on 11 December in Brussels. All project partners and the EC project officer met to commence the implementation of the work plan that had been agreed upon for the next two years.

PUBLICATIONS

MVVC

Illingworth J. et al. (2013). Chronic exposure to *Plasmodium falciparum* is associated with phenotypic evidence of B and T-cell exhaustion. The Journal of Immunology, 190(3): 1038-1047. doi: 10.4049/jimmunol.1202438.

Ndungu F. M. et al. (2013). Long-lived *Plasmodium falciparum* specific memory B cells in naturally exposed Swedish travellers. European Journal of Immunology, 43(11): 2919-2929. doi: 10.1002/eji.201343630.

Ogwang C. et al. (2013). Safety and immunogenicity of heterologous prime-boost immunisation with *Plasmodium falciparum* malaria candidate vaccines, ChAd63 ME-TRAP and MVA METRAP, in healthy Gambian and Kenyan adults. PLOS One, 8(3). doi: 10.1371/journal.pone.0057726.

IDEA

Labuda L. A. et al. (2013). Alterations in peripheral blood B cell subsets and dynamics of B cell responses during human schistosomiasis. PLOS Neglected Tropical Diseases, 7(3). doi: 10.1371/journal.pntd.0002094.

Petruccioli E. et al. (2013). IFN /TNF specific cells and effector memory phenotype associate with active tuberculosis. The Journal of Infection, doi: 10.1016/j.jinf.2013.02.004.

Goletti D. et al. (2013). Autophagy in *Mycobacterium tuberculosis* infection: A passepartout to flush the intruder out? Cytokine Growth Factor Reviews, 24(4): 335-343. doi: 10.1016/j.cytogfr.2013.01.002.

TRANSVAC

Kaufmann S. H. E. (2013). Tuberculosis vaccines: Time to think about the next generation. Seminars in Immunology, 25(2): 172-181. doi:10.1016/j.smim.2013.04.006.

Kaufmann S. H. E. and Dorhoi A. (2013). Inflammation in tuberculosis: interactions, imbalances and interventions. Current Opinion in Immunology, 25(4): 441-449. doi:10.1016/j.coi.2013.05.005.

Grode L. et al. (2013). Safety and immunogenicity of the recombinant BCG vaccine VPM1002 in a phase 1 open-label randomized clinical trial. Vaccine, 31(9): 1340-1348. doi:10.1016/j.vaccine.2012.12.053.

Weiner J. et al. (2013). The dual role of biomarkers for understanding basic principles and devising novel intervention strategies in tuberculosis. Annals of the New York Academy of Sciences, 1283: 22-29. doi:10.1111/j.1749-6632.2012.06802.x.

Misstear K. et al. (2013). Targeted nasal vaccination provides antibody independent protection against *Staphylococcus aureus*. The Journal of Infectious Diseases, doi: 10.1093/infdis/jit636.

EVI (INYVAX)

Bonhoeffer J. et al. (2013). Template protocol for clinical trials investigating vaccines – focus on safety elements. Vaccine, 31(47): 5602–5620. doi:10.1016/j.vaccine.2013.02.041.

INTERNATIONAL FORA AND EXTERNAL COMMUNICATIONS

Emerging and re-emerging infectious diseases: How prepared are we for the global threat? 2 March, Munich

The seminar was hosted by the Centre for International Health, targeting graduate and medical students, health professionals and researchers. The aim of the seminar was to understand the current situation in the field of emerging infectious diseases, their control mechanisms and the way forward, and to promote the exchange of ideas, encourage scientific debate and foster networking, partnerships and opportunities among experts in different fields. EVI was represented by Odile Leroy, who accepted an invitation to present "*Developments in vaccines for infectious disease*".

MVW 2013, 22–24 April, Lausanne

The third conference in the MVW series (MVW 2013) is the follow-up to the successful MVW meetings held in London in 2007 and Washington DC in 2010, offering researchers a fresh new forum to discuss the current status of new malaria vaccine initiatives, vaccine candidates and clinical trials. MVW 2013 focused on 'Vaccine Issues' in relation to malaria as a worldwide disease and attracted scientists, physicians and other professionals from the academic, industrial/commercial and governmental/policy/regulatory sectors interested in the development, assessment, trends and deployment of malaria vaccines. The conference was attended by Odile Leroy, who is a member of the MVW Scientific Advisory Panel, Babatunde Imoukhuede, Céline Dutruel, Nicola Viebig, Sophie Houard, Mark Geels and Nathalie Imbault.

PDP forum, Bill and Melinda Gates Foundation, 30 April-2 May, Seattle

Odile Leroy was invited through KfW, Germany to attend the PDP forum which gather all the PDPs receiving support from the BMGF. The main insight from the meeting was the presentation of the new strategy for malaria vaccine by Christopher Elias and Trevor Mundel. The focus of BMGF is much more aligned now with the niche of EVI on translational research, including discovery.

EDCTP NID stakeholders meeting, 27–28 June, The Hague

The objectives of the stakeholder meeting on NIDs were to:

- Review the current status and barriers to progress in the field of NIDs
- Identify the key research areas where EDCTP support is likely to have maximum impact
- Highlight opportunities for European and African collaboration (North-North and North-South) that can be facilitated by EDCTP
- Identify potential partnerships with likeminded organisations.

Odile Leroy gave a presentation entitled "*Vaccines for NIDs*".

EDCTP Malaria stakeholders meeting, 19–20 September, Vienna

The objectives of the EDCTP stakeholder meeting on malaria were to:

- Review the current status and barriers to progress in the field of malaria research
- Identify the key research areas where EDCTP support is likely to have maximum impact
- Highlight opportunities for European and African collaboration (North-North and North-South) that can be facilitated by EDCTP
- Identify potential partnerships with likeminded organisations.

Odile Leroy took part in a round table discussion.

6th MIM Pan African Malaria Conference, 6-11 October, Durban

MIM is a scientific malaria conference and the world's largest gathering of the malaria community, bringing together 1800 leading researchers, activists, health workers, public health officials and policymakers every three to four years. A symposium on "*The challenge of developing a pregnancy-associated malaria vaccine*" was organised by EVI, chaired by Alister Craig, Liverpool School of Tropical Medicine, UK, chair of EVI SAC, and co-chaired by Odile Leroy. Alister Craig was a plenary speaker. Nicola Viebig and Sophie Houard also attended the symposium.

Developing Countries' Vaccine Manufacturers' Network Annual General Meeting, 7–9 October, Hanoi

Nathalie Imbault represented EVI, and gave a presentation entitled "*Clinical trials networks*".

World Vaccine Congress 2013, 16–17 October, Lille

The 14th World Vaccine Congress is Europe's leading scientific and business development event for the vaccine industry, bringing together decision makers, influencers and end users from the pharmaceutical and biotechnology industries, as well as academia and government. Odile Leroy gave a talk entitled "*A world free of the intolerable burden of diseases of poverty*" and participated in the panel discussion "*Innovative vaccination roadmaps and collaborations for European research*".

7th Vaccine & ISV Congress, 27–29 October, Barcelona

The 7th Vaccine & ISV Congress featured science and public health topics, from primary vaccine research and vaccine manufacturers, to governmental policy, safety and regulation. Céline Dutruel gave a presentation entitled "*TRANSVAC - European network of vaccine research and development*".

ASTMH 61st Annual Meeting, 11–15 November, Washington DC

The ASTMH annual meeting is one of most important events of the year for those involved in tropical medicine, and the event is always well attended. A symposium to launch the updated MVTR was held on 15 November. EVI were represented by Ines Petersen, Stefan Jungbluth and Nathalie Imbault who gave a presentation at the symposium entitled "*EVI's updated strategy for malaria vaccine development based on the updated Roadmap*".

INTERNATIONAL GOVERNANCE

Governance

The year 2013 was yet again highly productive for the EVI governing bodies.

The EVI SAC met face to face once for the annual review of the portfolio in December, a closed meeting before and after the EVI Rendez-Vous. The EVI SAC also held two teleconferences on projects requiring specific attention.

A new member joined the eight existing members: Jim Robertson, chosen for his expertise in vaccines, regulatory and biological standards. At the EVI SAC meeting, Alister Craig was proposed as the chair with two vice chairs, Ingileif Jonsdottir and Jim Robertson. These recommendations were approved by the EVI Board, and the EVI Secretariat is honoured to have such a committed team of scientific experts.

The EVI Board also met three times: 1) for the first of the usual bi-annual meetings at the end of February, 2) for the review of the results of the EVI external review in August, and 3) for the second bi-annual meeting in December. Furthermore, after the departure of Dr Terry McWade, Chair of EVI Board, in the spring, Professor Ruairi Brugha, Professor and Head of the Department of Epidemiology and Public Health Medicine, and Head of the Division of Population Health Sciences at the RCSI, joined the EVI Board on 30 July. Before the election of Dr Clemens Kocken as chair of EVI Board on 5 December, Professor Marita Troye-Blomberg, vice-chair of EVI Board, kindly and efficiently acted as temporary chair. The EVI Secretariat and Board would like to thank Terry McWade for his support in strengthening EVI governance during his two year mandate as a Board member.

The EVI BoS met twice jointly with the EVI Board in February and December. Jean-Paul Prieels, MaSTerCell, Belgium, was elected as a member of the BoS at the February meeting of the EVI Board.

Further to recommendations from an external consultant, Michael Kelly from Empeira, the EVI Board has established a finance and risk management committee with three voting members: Clemens Kocken, BPRC, Martin Trillsch, UHEI, and Leo van der Pol, Intravacc. The EVI Secretariat has put in place risk management and internal audit functions. The second internal audit took place at the end of the year.

In addition, EVI has adopted a new document management system (Xerox DocuShare®) which has been in use since July. Almost all EVI documentation was successfully transferred to this online archiving system and the remaining documents was to be transferred in the first quarter of 2014. This system simplifies the archiving of different versions of the same document and provides the EVI Secretariat, Board, BoS and SAC with a "task assignment" tool enabling them to optimise the internal review of documents. It also allows the direct archiving of emails as PDF documents, together with their attachments.

Participants at EVI SAC, BoS and Board meetings

EVI-EEIG Board and BoS

25 March, face to face meeting, IWH, Heidelberg, combined with a BoS Meeting

EEIG Board:

Claire Boog, RIVM, the Netherlands

David Salisbury, Jenner Vaccine Foundation, UK

Clemens Kocken, BPRC, the Netherlands

Terry McWade (chair), RCSI, Republic of Ireland

Marita Troye-Blomberg (vice-chair), Stockholm University, Sweden

BoS:

Suresh Jadhav, SII, India

Sodiomon Bienvenu Sirima (chair), CNRFP, Burkina Faso

From EVI: Odile Leroy, Sten Larsen, and Nathalie Imbault (Secretary of EVI Board and BoS)

29 August, face to face meeting, Institut Pasteur, Paris

EEIG Board:

Ruairi Brugha, Clemens Kocken, Marita Troye-Blomberg (vice-chair, acting chair), Leo van der Pol (substitute for Claire Boog)

BoS:

Suresh Jadhav, Sodiomon Bienvenu Sirima (chair), Charles de Taisne, Sanofi Pasteur, France

From EVI: Odile Leroy, Sten Larsen, Nathalie Imbault (Secretary of EVI Board and BoS) and Jill Iversen

5 December, face to face, IWH Heidelberg, combined with a BoS Meeting

EEIG Board:

Ruairi Brugha, Clemens Kocken (chair), Martin Trillsch, Marita Troye-Blomberg (vice-chair), Sam McConkey (SAC, non-voting member)

BoS:

Patrick Empey, Irish Aid, Republic of Ireland, Suresh Jadhav, Sodiomon Bienvenu Sirima (chair), Charles de Taisne.

From EVI: Odile Leroy, Sten Larsen, Nathalie Imbault (Secretary of EVI Board and BoS) and Jill Iversen

EVI SAC

3–4 December, face to face meeting, IWH Heidelberg

Alister Craig (chair), Liverpool School of Tropical Medicine, UK

Guiseppe Del Guidice, Novartis Vaccines and Diagnostics, Research Center, Italy

David Goldbaltt, Institute of Child Health, University College London, UK

Ingileif Jonsdottir (vice-Chair), Landspitali University Hospital, Iceland

Samuel McConkey, RCSI, Republic of Ireland

James S. Robertson (vice-chair), Consultant, UK

Mahamadou Ali Thera, University of Bamako, Mali

Aissatou Touré, Institut Pasteur de Dakar, Senegal

EVI Secretariat

FUNDRAISING

In 2013, EVI together with other partner organisations successfully mobilised funds that allowed the initiation of several new projects related to vaccine development and science policy. A total of €16,577,889 was raised from the EC, the principal funder of the four new projects.

The EDUFLUVAC project will use a combinatorial immunisation strategy for the development of a universal influenza vaccine which aims to educate the immune system to cross-recognise common regions within multiple influenza virus strains, an approach which is expected to confer better protection against epidemic influenza. The second project, BELLEROPHON, will use an innovative tagging strategy leading to the oligomerisation of the antigen for the creation of an entirely novel vaccine against *Staphylococcus aureus* infections in humans. Finally, the IPROVE project is a policy project that will develop a roadmap to inform strategic decisions relating to the future of vaccine research and development in the EU.

The year 2014 will see the official launch of the new EC FP for Research and Innovation, Horizon 2020. EVI and its collaborating institutions successfully campaigned for the incorporation of certain research topics in the new programme and have already taken the lead in the preparation of several funding proposals in response to the first calls under Horizon 2020 published by the EC at the end of 2013.

In the context of its fundraising strategy, EVI continued its involvement in European and national-level advocacy to attract further funding for research and the development of products targeting diseases of poverty. These efforts will be strengthened in the future.

Table 1 – Summary of fundraising

Donor	Title	Total Amount	Total EVI
EC	Clinical Development of a var2CSA-based Placental Malaria Vaccine Candidate (PlacMalVac)	5,498,829	435,297
EC	Combining cellular and humoral immune responses as a vaccine strategy against *Staphylococcus aureus* pathogen (BELLEROPHON)	5,935,544	518,566
EC	Innovation partnership for a roadmap on vaccines in Europe (IPROVE)	496,367	78,067
EC	Combinatorial immunisation strategy to educate the immune system towards cross-recognition and coverage against antigenic drift in seasonal influenza virus exposure (EDUFLUVAC)	4,647,149	930,000
TOTAL Raised by EVI & partners:		*16,577,889*	*1,961,930*

ROADMAPS

Malaria Vaccine Technology Roadmap

Following an intense period of preparation, the WHO, together with EVI and other members of the MVFG, launched the updated MVTR[18] in November. In response to recent changes in malaria epidemiology and control, and acknowledging important developments in malaria research since the launch of the original roadmap in 2006, the strategic goals and priority areas were expanded and updated by the organisations involved in the development of this joint vision. Priority areas of the MVTR that were updated include the standardisation of assays, clinical trial designs and assessment, a commitment to making the results from all funded malaria vaccine trials publicly available within 12 months after the last subject visit, and a commitment to establish a systematic approach for the prioritisation of vaccine candidates, including malaria caused by *P. vivax* and *P. falciparum*.

Roadmap for the establishment of a European vaccine R&D infrastructure

In the context of the TRANSVAC project, EVI, the other project partners and additional stakeholders coordinated the preparation of a roadmap outlining the way towards the establishment of sustainable European vaccine R&D infrastructure in which the major vaccine R&D actors in Europe could be brought together to consolidate the integration of the increasingly fragmented European vaccine development landscape. The roadmap was finalised during 2013 and will serve as a reference document to guide national and European policy makers and funding bodies in their efforts to support such a venture.

[18] http://www.who.int/immunization/topics/malaria/vaccine_roadmap/TRM_update_nov13.pdf?ua=1

FINANCE

Table 2 - Financial statements as audited for the year

Profit and Loss	EUR 2013	EUR 2012
1. Turnover	250.00	800.00
2. Other operating income from donors	9,695,939.40	8,004,057.29
3. Miscellaneous operating income	0.00	0.00
4. Subtotal I	**9,695,939.40**	**8,004,857.29**
5. Personnel wages		
a. Wages and salaries	-1,013,898.27	-1,216,331.83
b. Social security costs	-239,931.60	-228,040.72
c. Thereof for pensions: EUR 0.00	0.00	0.00
	-1,253,829.87	**-1,444,372.55**
6. Depreciation on tangible fixed assets	-17,700.34	-14,111.40
7. Other operating expenses	-8,059,019.42	-5,807,185.40
8. Subtotal II	**365,389.77**	**739,187.94**
9. Other interest and similar income	12,935.10	8,124.11
10. Net result	**378,574.87**	**747,312.05**
11. Tax	0.00	0.00
12. Result after tax	**378,574.87**	**747,312.05**

Balance Sheet / Assets		EUR 2013		EUR 2012
Assets				
A. Fixed assets				
Tangible assets				
Other equipment, office and plant equipment		**32,899.03**		**44,948.98**
B. Current assets				
I. Other assets	5,784.83		14,820.30	
II. Cash in hand, cash in banks	6,235,688.64	**6,241,473.47**	4,106,846.20	**4,121,666.50**
C. Prepaid expenses				
I. Other prepaid expenses		**13,554.48**		**26,114.67**
		6,287,926.98		**4,192,730.15**

Balance sheet / Liabilities and Equity		EUR 2013		EUR 2012
A. **Equity**				
Reserves	747,312.05		0.00	
Net income	378,574.87		747,312.05	
		1,125,886.92		**747,312.05**
B. **Accruals**				
Other accruals		**537,163.27**		**280,615.05**
C. **Liabilities**				
1. Liabilities in relation to grants received				
a. National governments grants liabilities	2,867,275.20		2,444,781.34	
b. European Union and other restricted grant liabilities	1,222,367.05		315,991.72	
Thereof with a remaining term up to one year	4,089,642.25		2,760,773.06	
2. Creditors (trade liabilities)	501,031.63		340,796.01	
3. Other liabilities	34,202.91		63,233.98	
Thereof from taxes	20,431.10		25,912.54	

Balance sheet / Liabilities and Equity		EUR 2013		EUR 2012
Thereof from social security	918.31		-6,777.88	
Thereof with a remaining term of up to one year	34,202.91	**4,624,876.79**	63,233.98	**3,164,803.05**
		6,287,926.98		**4,192,730.15**

Financial Audit statement for the year ending 31 December 2013

To European Vaccine Initiative-EWIV, Heidelberg:

We have audited the annual financial statements, comprising the balance sheet, the income statement and the notes to the financial statements, together with the bookkeeping system of European Vaccine Initiative EWIV, Heidelberg, for the business year from January 1 to December 31, 2013. The maintenance of the books and records and the preparation of the annual financial statements in accordance with German commercial law and supplementary provisions in the statutes are the responsibility of the entity's management. Our responsibility is to express an opinion on the annual financial statements, together with the bookkeeping system, based on our audit.

We conducted our audit of the annual financial statements in accordance with Section 317 of the German Commercial Code and the German generally accepted standards for the audit of financial statements promulgated by the Institut der Wirtschaftsprufer (Institute of Public Auditors in Germany). Those standards require that we plan and perform the audit such that misstatements materially affecting the presentation of the net assets, financial position and results of operations in the annual financial statements in accordance with German principles of proper accounting are detected with reasonable assurance. Knowledge of the business activities and the economic and legal environment of the entity and expectations as to possible misstatements are taken into account in the determination of audit procedures. The effectiveness of the accounting related internal control system and the evidence supporting the disclosures in the books and records and the annual financial statements are examined primarily on a test basis within the framework of the audit. The audit includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the annual financial statements. We believe that our audit provides a reasonable basis for our opinion.

Our audit has not led to any reservations.

In our opinion, based on the findings of our audit, the annual financial statements as of December 31, 2013 of European Vaccine Initiative-EWIV, Heidelberg, comply with the legal requirements and the supplementary provisions in the statutes and give a true and fair view of the net assets, financial position and results of operations of the entity in the accordance with principles of proper accounting.

Heidelberg, den 4. April 2014

FALK GmbH & Co KG
Wirtschaftsprüfungsgesellschaft
Steuerberatungsgesellschaft

(Meyer)
Wirtschaftsprüfer

(Ahrens)
Wirtschaftsprüfer

FINANCIAL PRESENTATION

The year 2013 was again an exciting year for EVI. We have achieved promising results in vaccine development, with our projects progressing strongly through vaccine production and clinical testing. The EC/EDCTP projects have efficiently met substantial deliverables and milestones, as shown by the financial figures. The EVI Secretariat has, in the current reporting period, once again shown an astonishing and conscientiousness level of achievement in all areas of EVI activities. This year showed that progress can be made by applying good business acumen to the utilisation of EVI full funds. EVI is, as always indebted to its grant providers for their strong support, and the EVI Secretariat would like to extend heartfelt thanks to Irish Aid, BMBF, EDCTP and the EC for their invaluable encouragement.

Figure 1 shows the cost activity over the current reporting period, during which expenditure covering the broad portfolio of EVI, EDCTP and EC projects has technically produced major achievements in comparison with the level of funding. The financial conclusion of the current reporting period is that the performance of EVI has been unceasingly strong, and that funds are properly utilised to accelerate the development of vaccines against diseases of poverty.

Figure 1 - Total EVI Activity 2013

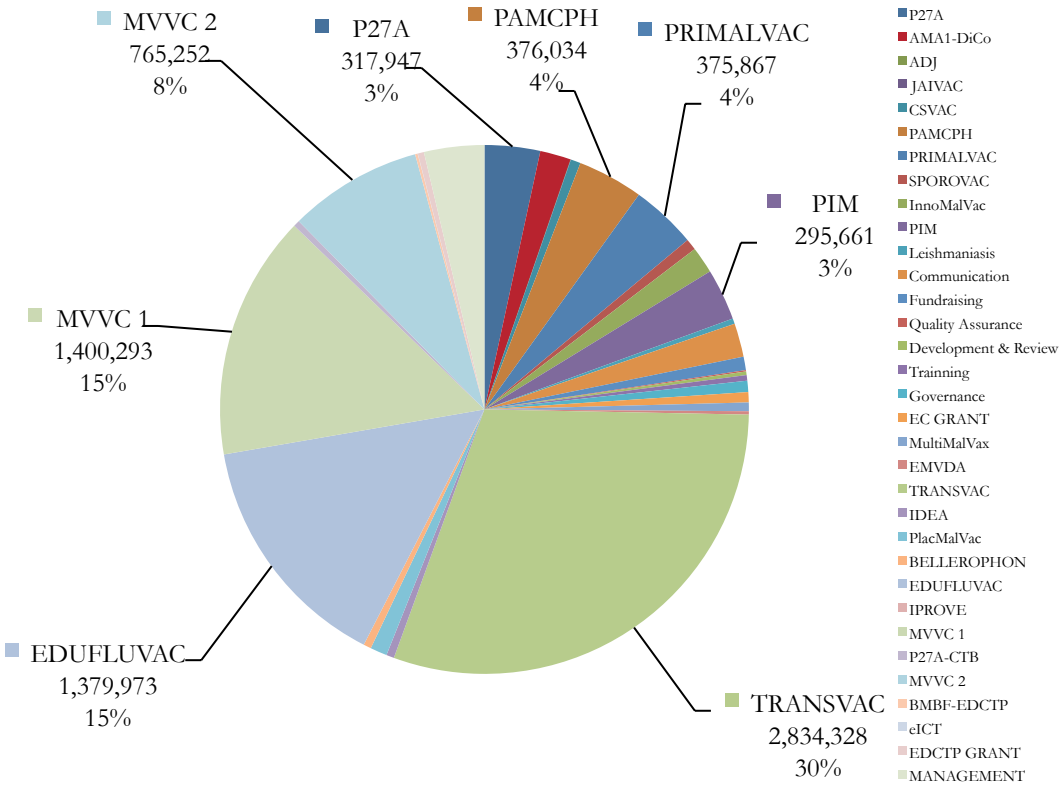


Table 3 - Key Ratios

The following key ratios result from EVI's 2013 operations.

Management Percentage			
Year	Decided threshold	Result	Direct investment percentage of each EURO donated
2011	7.00%	4.02%	**96%**
2012	7.00%	2.20%	**98%**
2013	7.00%	3.70%	**96%**

For each euro donated to EVI, almost 97% is, on average, directly invested into vaccine development against poverty related diseases.

Table 4 - Quick Ratios

Indicators	**Ratios' Results**	
	Figure	**Qualification**
Quick ratio (liquidity)	6.02	Good
Gross operating profit ratio (financial autonomy)	0.00	Good
Profitability	1,532.36	Good
Solvency	4.58	Acceptable

Indicators	**Noteworthy Value's Result**	
	Figure	**Qualification**
Equity flag	4.58	Good

Purpose	**Indicators**	**Weak* 0**	**Acceptable* 1**	**Good* 2**
Liquidity	Quick ratio	$i < 0.5$	$0.5 \leq i \leq 1$	$i > 1$
Financial autonomy	Gross operating profit ratio	$i > 0.40$ or <0	$0.40 \geq i \geq 0.30$	$0 \leq i < 0.30$
Profitability	Profitability	$i < 0.05$	$0.05 \leq i \leq 0.15$	$i > 0.15$
Solvency	Solvency	$i > 6.00$ or < 0	$6.00 \geq i \geq 4.00$	$0 \leq i < 4.00$
Purpose	**Indicators**	**Weak**		**Good**
Equity flag	Solvency	$i > 10.00$ or < 0		$i \leq 10.00$ and ≥ 0

* Qualifications as decided by the EC

Table 5 - Summary of other important ratios**

Indicator	Figure	Explanation
RoA on EVI Grants signed***	**866%**	Grants effect (signed grants) on core donations to EVI
RoA on EVI investment core projects***	**418%**	Four times earmarked funds raised for EVI projects for each core euro donation
RoA on core donations for EVI Secretariat***	**2955%**	Equivalent to 29½ times more funds raised for all earmarked purposes for each core euro donation

** The RoA percentage shows how efficiently EVI uses its assets in generating new revenue

***Achieved in the period 2006–2012

Table 6 - Key financial indicators

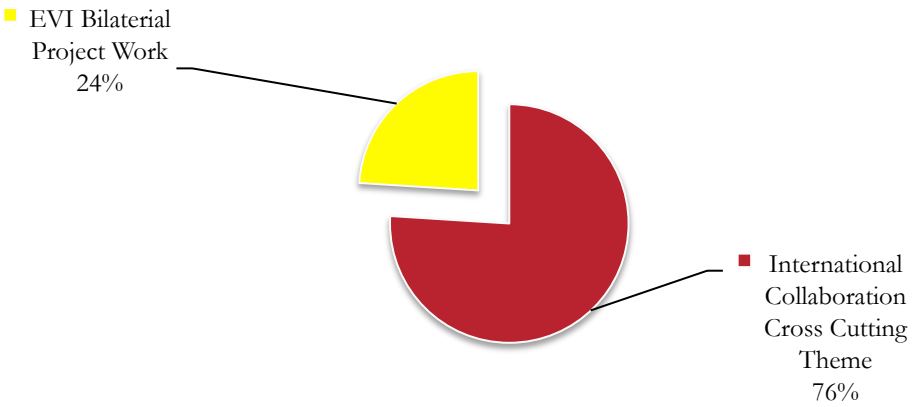
The following key indicators result from EVI's 2013 operations

Annual growth margin	$\frac{\text{Current period} - \text{Previous period}}{\text{Previous period}}$	21%
Annual OPEX (operating expenses)	$\frac{\text{OPEX for the period}}{\text{Net Revenue for the period}}$	83%
Working capital as percentage of revenue	$\frac{\text{Total Current Assets} - \text{Total Current Liabilities}}{\text{Net Revenue for the quarter} \times 4}$	285%
Return on assets	$\frac{\text{Net Income for the quarter} \times 4}{\text{(Beginning-of-quarter Total assets + End-of-quarter Total Assets)/2}}$	7%
Return on equity	$\frac{\text{Net Income for the quarter} \times 4}{\text{(Beginning-of quarter Total S/E + End-of-quarter S/E)/2}}$	20%

International collaboration

In 2013, 76% of EVI activities were direct international collaborations with partners and stakeholders from Europe, Africa, Asia and North America, whereas 24% represented bilateral work, which by its nature also counts as international collaboration (see Figure 2).

Figure 2 - International collaborations (in %)



EVI project activities

Over the past year, the activity of the EVI vaccine portfolio has increased, with ongoing cGMP manufacturing and clinical trials progressing surely and steadily.

Figure 3 - EVI portfolio investment (€'000 and in %)

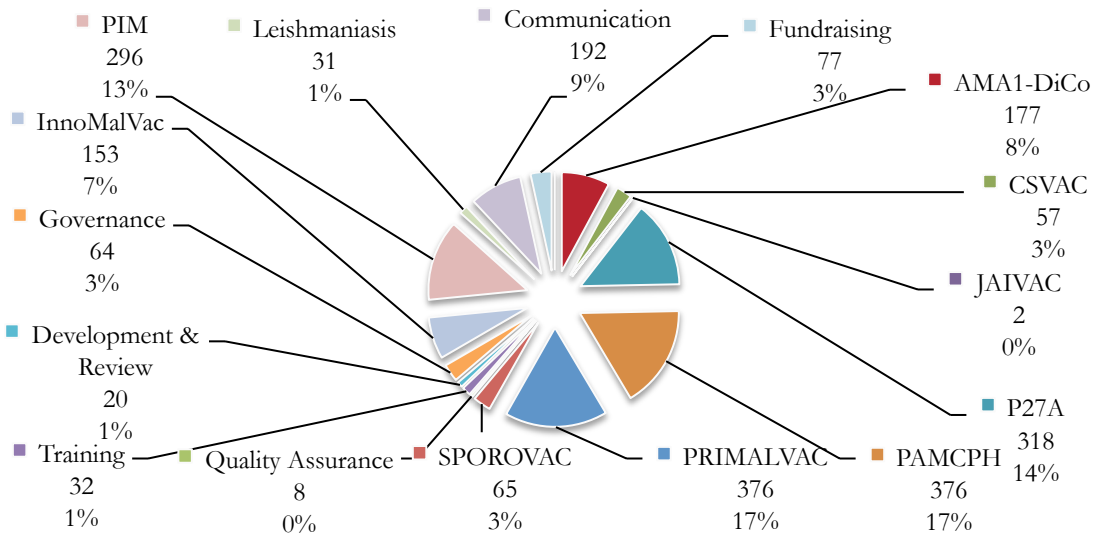
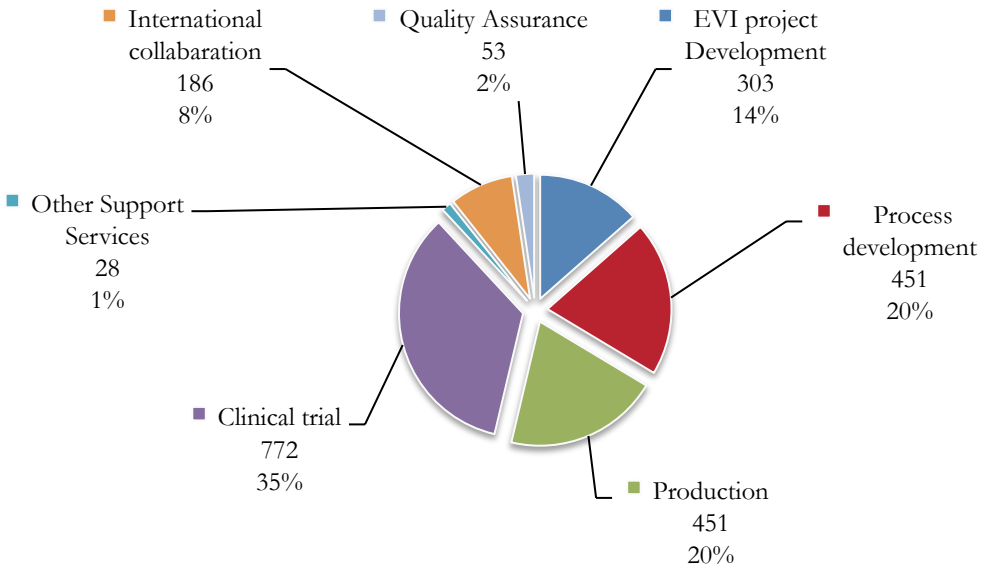


Figure 3 shows that investment over the past year has been dominated by cGMP production and clinical trials (up to 55%). Investment over the next year will continue to be dominated by cGMP production and clinical trials, especially for the PAM projects.

Figure 4 - Portfolio investment type (€'000 and in %)

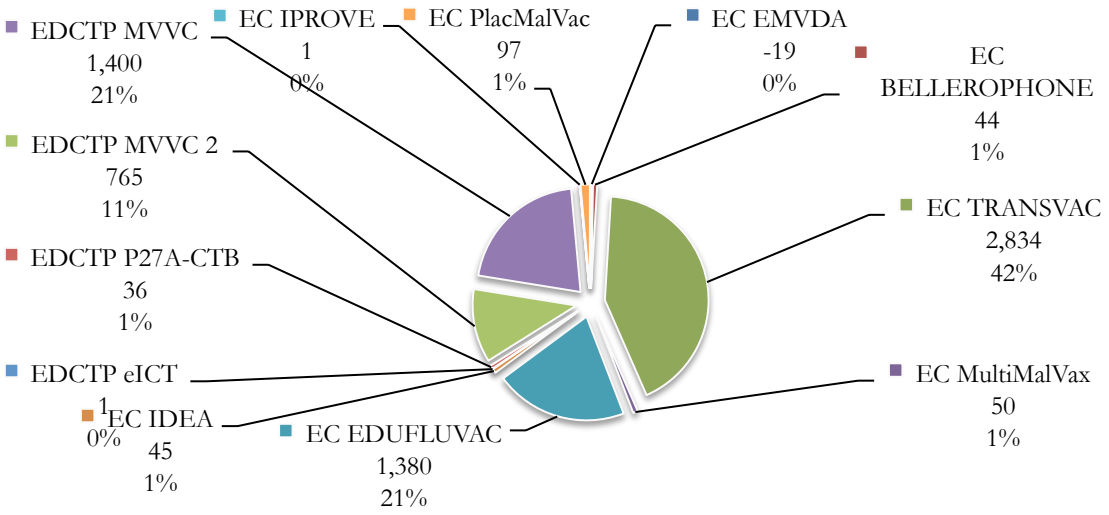


EVI EC and EDCTP activities

Besides the EVI portfolio of specific investment in various vaccine candidate projects, EVI is also involved in several EC and EDCTP funded projects.

Figure 5 shows the expenditure on all these projects.

Figure 5 - EC and EDCTP activity (€'000 and in %)

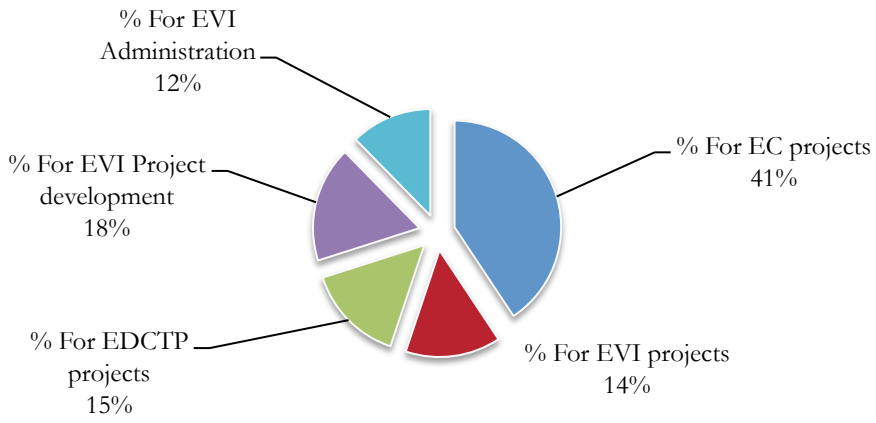


Staff time hours in the current reporting period

In 2013, EVI managed to keep up the pace on the EC and EDCTP projects as reflected in Figure 6. Although staff spent 12% of their time on administration, overall management expenditure only accounted for 3.7% of global expenditure.

By the end of 2013, most personnel were based at the EVI Headquarters in Heidelberg, Germany and only three staff members were placed outside of Germany, two of whom worked at the registered office in Denmark. EVI's strategy to strengthen the executive office and continue to reduce expenditure on consultants was continued effectively in 2013.

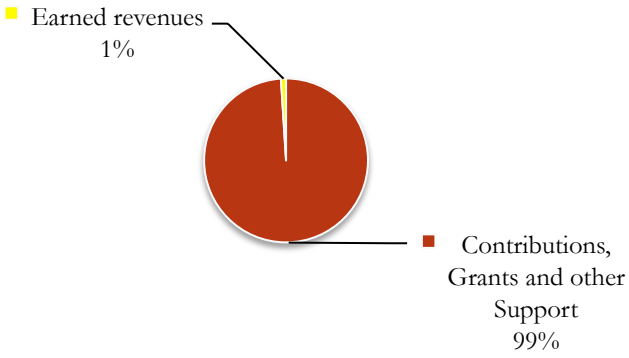
Figure 6 - Staff time - hours (in %)



Income and expenditure composition

EVI's income consists almost entirely of public funding from the EC, European Union Member States government grants and EDCTP, with only 1% from other source in 2013.

Figure 7 - Income composition (in %)



EVI's expenditure primarily reflects the outsourcing of production and clinical trials. Secondary costs include the payroll, which is strongly linked to the EC and EDCTP projects and of course EVI core vaccine projects.

EVI made considerable payroll savings in 2013, which decreased from 20% of the total costs in 2012 to 13% of the total costs in 2013. EVI continues to have a strict travel policy, which has kept the travel costs at 4%.

Figure 8 - Expenditure composition (in %)

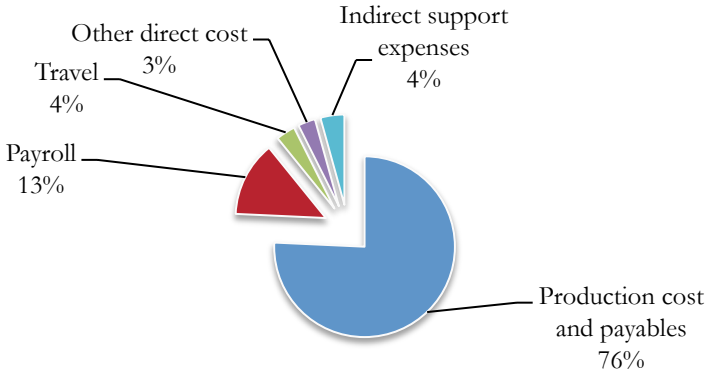


Table 7- Financial audit

The following financial audits were performed during the current reporting period:

Completed by FALK & Co	
DGIS grant financial audit 2012	Successful, No qualifications
BMBF grant financial audit 2012	Successful, No qualifications
TRANSVAC project financial audit 2012-2013	Successful, No qualifications
EVI organisational audit 2012	Successful, No qualifications
Continued internal control by Prentis & Co.	
Internal Control	Successful, No qualifications

FINANCIAL NOTES 2013

Principal accounting policies

(a) General comment

EVI fully lives up to the demands of German General Accepted Accounting Principles (GAAP) and empowers its staff working on projects to participate continuously in budget and spending control. Taking its size into consideration, EVI does much more financial controlling than legally required to meet the highest standards. EVI operates an extensive and continuous internal control system for financial management in order to achieve the highest standards of public funds management. EVI operates a sharp diversification of financial tasks and, despite having a relatively small Secretariat, ensures the extensive and detailed controlling of all transactions by staff in the Finance Unit, the Executive Director and the empowered project leaders. EVI carefully monitors its liquidity and plans its fundraising activities to ensure liquidity years in advance as part of its risk management strategy. EVI set up and developed AESIRAS accounting, which now operates as the accounting and financial management tool for EVI/non-profit business with an astonishing four dimensional accounting/analysis programme and matrix account analysis tool.

(b) Basis of accounting

The basis of accounting is the German GAAP. Other accounting policies are described in the EVI handbook, and rules of procedures together with relevant policies known and applied by EVI staff. EVI accounting method is accrual based, with consideration for projects governed by external guidelines.

(c) Funding parties

EVI is currently funded by government agencies (Irish Aid, BMBF) and the EC in addition to the EDCTP.

EVI is always open to new donors and private funders who share EVI's vision of a world free from the burden of diseases of poverty, or who wish to support a good cause that will combat poverty.

(d) Realised income policy

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

(e) Payables

All amounts payable by EVI are charged to the PNL in the cost-relevant year on the basis of accrual accounting. Payables are identified, evaluated and approved by the relevant project leaders for proof of deliverables and milestones. The Finance Unit then attributes them to the relevant accounts, and dimensions segmented by defined details.

(f) 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.

(g) Primary and secondary commerce

EVI's primary focus is to develop vaccines that combat diseases of poverty. As a secondary source of income, EVI may offer services such as lecturing, workshops and debates where needed as well as using any surplus of product to the fullest extent.

(h) Funds accounting

Funds held by EVI are either:

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

• Earmarked (restricted) funds – these are funds related to specific earmarked projects including EC/EDCTP and other similar projects

(i) Time recording

EVI operates, on daily basis, a comprehensive time management recording system that fully lives up to the demands of public management, with the emphasis on transparency, accountability and accuracy. The system identifies every productive staff hour, which are segmented in defined dimensions in detail and accounted into the financial system as such.

(j) Budget planning

Budget planning is performed by the Finance Director each year – with the support of the project leaders who are responsible for reporting and planning their own areas of responsibility in detail. The Finance Director receives and compiles the overall budget and presents it to the Executive Director who in turn reports the budget to the EVI-EEIG Board through a work plan proposal.

(k) Equity

Funds held by EVI as equity are utilised as strategic reserves for R&D for the organisation. EVI does not pay out any dividends or similar benefits to its shareholders by order of the statutes of the organisation.

(l) Foreign currencies

Transactions in foreign currencies are translated into euro at rates prevailing on the date of the transaction using xe.com, with the exception of Danish Kroner which is politically fixed at a rate of 7.45. During 2013, EVI made use of the following currencies: EUR, DKK, INR, USD, GBP and XOF.

(m) Auditors

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

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

The current annual report includes the conclusion – the auditor's opinion – together with the audited PNL and balance sheet. The opinion is shown in German and an English translation is prepared by the auditor.

In addition, EVI has outsourced its internal control to Prentis & Co, Cambridge, UK.

(n) Final remarks and thanks

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 the UK for well-organised payroll management and tax advice. EVI would like to thank our internal controllers from Prentis & Co and FALK & co for their role as external financial auditors of EVI, both for the annual audit and for individual projects, which optimises EVI's performance.

Table 8 - Donations and grants received

BMBF / KfW	€	925,626
BMBF / EDCTP	€	28,977
EC BELLEROPHON	€	285,211
EC EDUFLUVAC	€	1,781,407
EC IDEA	€	57,177
EC MultiMalVax	€	134,167
EC TRANSVAC	€	3,173,001
EC PlacMalVac	€	239,413
EDCTP MVVC1	€	1,178,090
EDCTP MVVC2	€	826,061
EDCTP P27A-CTB	€	134,948
Irish Aid	€	2,000,000
DGIS	€	576,722

Table 9 - Interest earned

Interest Danish Account	€	77
Interest German Accounts	€	11,773
Exchange Gain	€	1,085
Total	€	12,935

EVI extends its thanks and appreciation to all its donors and grant providers.

Table 10 - Staff overview - List of staff as of 31 December 2013

First Name	Last Name	Title/Function in EVI	Location
Odile	Leroy	Executive Director	Germany
Mark	Geels	Project Manager	Germany
Nathalie	Imbault	Quality Assurance, External Relations & Communication, Director	Germany
Roland	Kleine	Office Clerk	Germany
Thorsten	Kohaut	Finance Manager	Germany
Nicola	Viebig	Project Manager	Germany
Celine	Dutruel	Project Manager	Germany
Ines	Petersen	Project Manager	Germany
Stefan	Jungbluth	Business Manager	Germany
Nicolas	Havelange	Production, Director*	Belgium
Sophie	Houard	Vaccine Development Manager	Belgium
Flavia	D'Alessio	Project Manager	Germany
Sten	Larsen	Finance & Human Resource, Director	Denmark
Jill	Iversen	Web Master*	Denmark
Regitze Louise	Thoegersen	Program Manager	Denmark
Harry	Van Schooten	Public Health and Business Development Advisor*	The Netherlands

*Consultant

Male	7
Female	9

Total Staff of EVI 31 December 2013 **16 (11.84 FTE)**

Table 11 - Income and Expenses

Income realised		
Contributions, grants and other support		
Revenue from indirect contributions	€	491,058
National government agency grants	€	2,569,910
EU grants	€	4,431,970
EDCTP grants	€	2,203,000
Total contributions, grants and other support	**€**	**9,695,939**
Earned revenues		
Interest-savings/short-term investments	€	12,935
Non-inventory sales – gross	€	250
Total earned revenues	**€**	**13.185**
Total income realised	**€**	**9,709,125**
Direct and indirect project expenditure **		
Grants, contracts and direct assistance		
Contracts - program-related	€	1,593,497
Benefits paid to or for MVVC consortium members	€	1,956,371
Benefits paid to or for EC consortium members	€	3,516,073
Total payables	**€**	**7,065,941**
Salaries and wage expenses		
Salaries and wages, international staff	€	232,137
Salaries and wages, German staff	€	438,188
Social maternity refunds	€	-26,520
Employee benefits and social security	€	872
Payroll taxes, etc.	€	296,052
In-house consultancies.	€	75,882
Statutory social security expenses	€	239,932
Contributions to health and safety agency	€	759
Voluntary social benefits not subject to wage tax	€	5,411
Employee benefit expenses	€	1,232
Holiday pay accrued	€	-10,115

Total salary cost	**€**	**1,253,830**
Contract service expenses		
Accounting fees	€	79,158
Accounting fees – SUB*	€	7,000
Legal fees	€	21,480
Professional fees - other	€	36,931
Facility & equipment maintenance expenses		
Software licenses	€	14,076
Software licenses – SUB*	€	2,345
Repairs and maintenance	€	17,736
Publishing cost including copy and printing	€	12,230
Publishing cost including copy and printing – SUB*	€	3,427
Books, subscriptions, references	€	1,117
In-house publications	€	2,258
Equipment, hardware and software		
Minor hardware purchases	€	902
Minor software purchases	€	1,151
Minor furnitures, fixed equip, vehicle parts	€	283
Depreciation and amortisation	€	17,700
Travel and meetings expenses		
Travel (flights)	€	138,631
Travel (train, ferry, taxi, other)	€	38,357
Travel (refund for use of own travel means)	€	2,128
Hotel and other accommodation costs	€	64,129
EC hotel and other accommodation costs	€	1,543
Conferences, conventions, meetings	€	26,892
EC conferences, conventions, meetings	€	8,464
EC conferences, conventions, meetings – SUB	€	1,400
EDCTP conferences, conventions, meetings	€	9,562
Travel allowances for employees	€	17,283
Restaurant, catering and other travel provisions	€	5,935
EC restaurant, catering and other travel provisions	€	5,038

External staff training costs	€	3,029
Total travel cost	€	**322,391**
Other direct expenses		
Insurances	€	16,842
Membership dues - organisation	€	183
Internal staff training costs	€	11,291
Advertising expenses	€	28,340
Contingency provisions	€	-65
Indirect business expenses		
Cleaning costs	€	53
Telephone and telecommunications	€	24,011
Broadband and other internet connections	€	1,331
Postage and shipping	€	9,610
Office Supplies	€	7,609
Printing and copying	€	555
Fees and charges	€	12,476
Hosting agreement costs	€	65,000
Fines, penalties, judgements	€	10
Organisational (corporate) expenses	€	279,744
EVI Board, BoS and SAC expenses		
Board travel cost	€	1,260
BoS travel cost	€	109
SAC meetings	€	3,800
SAC travel cost	€	3,652
EC ESAC, SAC and SC expenses		
SAC travel cost	€	2,884
SAC meetings	€	1,069
SAC travel cost	€	829
Total expenses	**€**	**9,330,550**

Result of the year

2013 Result:

Transferred to Equity – Reserved for R&D	€	**378,575**

** SUB is subcontracted cost as according to EC guidelines*

*** Expenditures as per account – for identified by project relevance see - expenditures by project table.*

Table 12 - Major payables

EVI project payments	Project relevance		Amount
Output	AMA1/P27A	€	38,728.23
GFA	AMA1	€	219.90
Voisin	PAMCPH	€	1015.00
R. Walt	SPOROVAC	€	15,730.03
Novalabs	AMA1	€	11,281.82
C.A.T.	P27A	€	1000.00
Barry Garfinkle	SPOROVAC	€	5760.02
Confarma	AMA1	€	-24,819.73
Fraunhofer	AMA1	€	30,319.99
Eltium	AMA1	€	1740.18
Almac	P27A	€	63,616.40
Inserm	AMA1	€	299,072.33
CHUV	P27A	€	154,500.00
UCPH	PAMCPH	€	350,000.00
GTP	PRIMALVCA	€	38,770.60
UOXF	InnoMalVac/PIM	€	442,500.00
RCSI	CSVAC	€	49,999.00
IDRI	AMA1/P27A	€	109,632.93

EDCTP project payments	Project relevance	Period		Amount
UOXF	MVVC2	2013-4	€	53,625.00
Okairos	MVVC2	2013-4	€	2998.88
Novartis	MVVC2	2013-4	€	2998.88
MRC Gambia	MVVC2	2013-4	€	50,488.35
CNRFP	MVVC2	2013-4	€	306,036.23
UCAD	MVVC2	2013-4	€	205,214.45
KEMRI	MVVC2	2013-4	€	66,317.63
KHRC	MVVC2	2013-4	€	69,712.50

MRC Gambia	MVVC1	2013-6	€	104,695.65
Okairos	MVVC1	2013-6	€	2955.63
KEMRI	MVVC1	2013-6	€	295,454.37
UCAD	MVVC1	2013-6	€	140,681.63
CNRFP	MVVC1	2013-6	€	655,127.21

EC project payments	**Project relevance**	**Period**		**Amount**
UOXF	EMVDA	2013-1	€	-5372.20
PB	EMVDA	2013-1	€	-7499.77
MRC	EMVDA	2013-2	€	-49.69
SSI	EMVDA	2013-2	€	-6231.38
MPIIB	TRANSVAC	2013-6	€	58,488.15
LIONEX	TRANSVAC	2013-6	€	270,202.64
VPM	TRANSVAC	2013-6	€	1889.00
HZI	TRANSVAC	2013-6	€	242,022.85
TBVI	TRANSVAC	2013-6	€	30,783.09
CVI	TRANSVAC	2013-6	€	141,828.53
UNIL	TRANSVAC	2013-6	€	290,402.05
UOXF	TRANSVAC	2013-6	€	274,096.01
LSHTD	TRANSVAC	2013-6	€	102,807.92

Table 13 - Expenditures by project

Project code	Amount spent (incl. partner pay)	In percentage
P27A	€ 317,947.01	3.41%
AMA1-DiCo	€ 177,318.16	1.90%
ADJ	€ 5.29	0.00%
JAIVAC	€ 1645.75	0.02%
CSVAC	€ 56,942.43	0.61%
PAMCPH	€ 376,034.09	4.03%
PRIMALVAC	€ 375,867.36	4.03%
SPOROVAC	€ 64,822.99	0.69%
InnoMalVac	€ 152,911.64	1.64%
PIM	€ 295.660.77	3.17%
Leishmaniasis	€ 31,130.44	0.33%
- - - - - -	- - - - - -	- - - - - -
Communication	€ 192,180.11	2.06%
Fundraising	€ 77,035.27	0.83%
Quality Assurance	€ 7702.33	0.08%
Development and Review	€ 20,488.55	0.22%
Training	€ 32,091.35	0.34%
Governance	€ 64,441.02	0.69%
- - - - - -	- - - - - -	- - - - - -
EC GRANT	€ 58,475.63	0.63%
MultiMalVax	€ 49,718.90	0.53%
EMVDA	-€ 19,153.04	-0.21%
TRANSVAC	€ 2,834,327.93	30.38%
IDEA	€ 44,641.09	0.48%
PlacMalVac	€ 96,663.12	1.04%
BELLEROPHON	€ 44,077.16	0.47%
EDUFLUVAC	€ 1,379,972.81	14.79%
IPROVE	€ 137.98	0.00%
- - - - - -	- - - - - -	- - - - - -
MVVC 1	€ 1,400,293.09	15.01%
P27A-CTB	€ 36,028.31	0.39%
MVVC 2	€ 765,.252.39	8.20%
BMBF-EDCTP	€ 14,440.60	0.15%

Project code		Amount spent (incl. partner pay)	In percentage
eICT - EDCTP	€	1426.70	0.02%
EDCTP GRANT	€	35,146.64	0.38%
------		------	------
Management	€	344,875.76	3.70%
TOTAL	€	9,330,549.63	100.00%

Table 14 - Balance overview of donor and EC/EDCTP funds (in €)

Donator/Grant	Type	Balance 31/12 2012	Received 2013	Cost 2013	Balance 31/12 2013
Irish Aid - IE	Core	**- 858,387**	2,000,000	1,595,980	**- 454,367**
Board Funds - EVI	Core	**3,226,930**	0	150,205	**3,076,725**
BMBF/KfW - DE	Restricted	**426,019**	925,626	803,445	**548,200**
BMBF - DE	Restricted	**0**	28,977	14,441	**14,536**
DGIS - NL	Restricted	**- 595,919**	576,722	-19,197	**0**
TRANSVAC - EC	Restricted	**- 492,940**	3,173,001	2,834,327	**- 154,266**
EDUFLUVAC – EC	Restricted	**0**	1,781,407	1,379,973	**401,434**
BELLEROPHON – EC	Restricted	**0**	285,211	44,077	**241,134**
PlacMalVac – EC	Restricted	**0**	239,413	96,663	**142,750**
IDEA - EC	Restricted	**- 6,248**	57,177	44,641	**6288**
EMVDA - EC	Restricted	**- 19,153**	0	-19,153	**0**
MultiMalVax - EC	Restricted	**- 26,349**	134,167	51,303	**56,515**
IPROVE – EC	Restricted	**0**	0	138	**-138**
MVVC - EDCTP	Restricted	**32,238**	1,178,090	1,400,292	**-189,964**
eICT – EDCTP	Restricted	**1,228**	0	1426	**-198**
MVVC2 – EDCTP	Restricted	**- 1,707**	826,061	765,252	**59,102**
P27A-CTB - EDCTP	Restricted	**- 1,944**	134,948	36,029	**96,975**
Administration	Core	**761,012**	504,399	1,020,494	**244,917**
Equity Reserves	Core	**747,312**	378,575	0	**1,125,887**
Total core		**3,876,867**	**2,882,974**	**3,892,566**	**2,867,275**
Total restricted		**- 684,775**	**9,340,800**	**7,433,658**	**1,222,367**
Total EVI funds		**3,192,092**	**12,223,774**	**11,326,224**	**4,089,642**

Table 15 - EVI inventory value estimated

P27A	€	152,684.00
AMA1-DiCo	€	278,397.00
ADJUVANTS	€	181,335.00
TOTAL	**€**	**612,416.00**

The assets created are meant to be for free as part of clinical trials, however where surplus exists it can be used for other purposes.

Value is based on lowest market rate estimated – the value does not appear as assets for the company since its primary use is for clinical trials – given for free.

Table 16 - EVI finished production inventory

Inventory ID	Name	Product type	Description	Batch number	Stock 01/01/13	Changes 2013	Quantity 31/12/13
NOVALABS	ALMy001	P27A Vaccine	P27A Line A	ALMy001	885	0	885
NOVALABS	ALMy001	P27A Vaccine	P27A Line B	ALMY001	822	0	822
NOVALABS	EVIy003	AMA1 - DiCo Vaccine	pfAMa1 DiCo 60 µg Lyophilised	EVIy002	1079	-108	971
NOVALABS	EVIy002	Adjuvant ALUM	Alhydrogel Line A	EVIy003	1728	-62	1666
NOVALABS	EVIy002	Adjuvant ALUM	Alhydrogel Line B	EVIy003	1712	-116	1596
OUTPUT GmbH	GLA-SE 20u/ml	Adjuvant-IDRI - Mixed	20uu/ml. 4% Oil - 0.4ml/Vial	0054-10F002	42	0	42
OUTPUT GmbH	GLA-SE 0.1mg/ml	Adjuvant-IDRI - Non Oil	0.1 mg/ml - 1 ml/Vial	QF547	18	0	18
OUTPUT GmbH	EM060G 4% oil, 0.4 ml	Adjuvant-IDRI - OIL	4% oil, 0.4 ml - 0.4ml/Vial	0038-10F001	185	0	185
OUTPUT GmbH	PfAma1-DiCo1	AMA1 - DiCo Vaccine	Bulk drug Substance	101108	11	0	11
OUTPUT GmbH	PfAma1-DiCo2	AMA1 - DiCo Vaccine	Bulk drug Substance	101115	10	0	10
OUTPUT GmbH	PfAma1-DiCo3	AMA1 - DiCo Vaccine	Bulk drug Substance	101122	7	0	7
OUTPUT GmbH	MTA Adjuvant	P27A Vaccine	20uu/ml. 4% Oil - 0.4ml/Vial	-	0	116	116

Inventory ID	Name	Product type	Description	Batch number	Stock 01/01/13	Changes 2013	Quantity 31/12/13
OUTPUT GmbH	MTA Adjuvant	P27A Vaccine	4% oil, 0.4 ml - 0.4ml/Vial	-	0	87	87
OUTPUT GmbH	DiCo MTA Adjuvant	AMA1 DiCo Vaccine	20uu/ml. 4% Oil - 0.4ml/Vial	-	0	65	65
OUTPUT GmbH	MTA Adjuvant	AMA1 DiCo Vaccine	4% oil, 0.4 ml - 0.4ml/Vial	-	0	65	65

Cash management (bank accounts)

Cash in German Key Accounts (EUR)	6,141,017.96
Cash in German Secondary Account (EUR)	38,252.76
Cash in Danish Bank (EUR)	54,675.41
Cash in UK Bank (EUR)	1,742.51

Hosting costs

EVI is hosted by the UHEI with the following costs:

Hosting costs – Legal support €65,000

Total 2013 service charges €65,000.00 (2012 = €65,000.00)

Remuneration of governing bodies

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

We formally sign and approve the EVI Annual Financial Report for the year 2013 ending 31 December 2013 in accordance with the 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 : / / 2014

Sten Larsen, EVI Finance Director

Date : / / 2014

Odile Leroy, EVI Executive Director

Date : / / 2014

Clemens Kocken, Chair of EVI-EEIG Board

Acknowledgement

The EVI Secretariat offers its thanks to the following people, who have contributed significantly to the success of EVI, especially all the participants in the clinical trials funded by EVI.

EVI Board members, and representatives of EVI donors

Alessandra	Martini	Belgium
Andrea	Holzäpfel	Germany
Ann	Uustalu	Belgium
Andreas	Holtel	Belgium
Annie	Vestjens	The Netherlands
Brian	Greenwood	UK
Charles	de Taisne	France
Charles	Mgone	Tanzania
Christian	Desaintes	Belgium
Christos	Profilis	Greece
Claire	Boog	The Netherlands
Claus	Bartram	Germany
Clemens	Kocken	The Netherlands
David	Salisbury	United Kingdom
Detlef	Böcking	Germany
Diarmuid	McClean	Republic of Ireland
Diarmuid	O'Donovan	Republic of Ireland
Hannu	Laang	Belgium
Hilde	Waelkens	Belgium
Inmaculada	Penas-Jimenez	Belgium
Irene	Plank	Belgium
Jean	Marie Habarugira	The Netherlands
Jean-Emmanuel	Faure	Belgium
Jean-Paul	Prieels	Belgium
Lucia	Bizonova	Belgium
Marita	Troye-Blomberg	Sweden
Marja	Esveld	The Netherlands
Michele	Ciavarini-Azzi	Belgium
Petra	Tonova	Belgium
Sodiomon	Sirima	Burkina Faso
Ruairi	Brugha	Ireland

Suresh	Jadhav	India
Terry	McWade	Republic of Ireland

SAC members

Aissatou	Toure	Senegal
Alister	Craig	UK
David	Goldblatt	UK
Giuseppe	Del Giudice	Italy
Ingileif	Jonsdottir	Iceland
James	Robertson	UK
Joachim	Hombach	Switzerland
Juhani	Eskola	Finland
Mahamadou Aly	Thera	Mali
Marie-Paule	Kieny	Switzerland
Roland	Dobbelaer	Belgium
Samuel	McConkey	Republic of Ireland
Shabir	Madhi	South Africa

Partners

Academisch Medisch Centrum bij de Universiteit van Amsterdam	NL
Academisch Ziekenhuis Leiden – Leids Universitair Medisch Centrum	NL
Agence nationale de recherches sur le sida et les hépatites virales	FR
Albert Schweitzer Hospital	GA
ALMAC Sciences	UK
Biomedical Primate Research Centre	NL
BIOTEM	FR
Central Veterinary Institute	NL
Centre Hospitalier Universitaire Vaudois	CH
Centre National de Recherche et de Formation sur le Paludisme	BF
Centre d'investigation clinique Cochin-Pasteur	FR
CiToxLAB	FR
CMC Biologics A/S	DK
Confarma	FR
Department of Health (former Health Protection Agency)	UK
Eberhard-Karls Universität Tübingen	DE

Ecole Polytechnique Federale de Lausanne	CH
Etna Biotech	IT
EuroVacc Foundation	NL
Evening Bay	BE
ExpreS2ion Biotechnologies	DK
Fondation international de l'Hopital de Dr Albert Schweitzer de Lambarene	GB
Fraunhofer IME	DE
Gregory Fryer Associates Ltd	UK
GTP technology	FR
Helmholtz Zentrum für Infektionsforschung GmbH	DE
Henogen Novasep	BE
Ifakara Health Institute	TZ
Imaxio SA	FR
Infectious Diseases Research Institute	USA
Institut de recherche pour le développement	FR
Institut national de la santé et de la recherche médicale	FR
Institut Pasteur	FR
International Centre for Genetic Engineering and Biotechnology	IN
Instituto de Biologia Experimental e Tecnológica	PT
Instituto Nazionale Malattie Infettive L.Spallanzani	IT
ISCONOVA	SE
Jenner Institute	UK
Kenya Medical Research Institute	KE
Kintampo Health Research Cemtre	GH
LIONEX GmbH	DE
London School of Hygiene and Tropical Medicine	UK
Ludwig-Maximilians-Universitaet München	DE
Malaria Consortium LBG	UK
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 Biological Standards and Control, a centre of the Medicines and Healthcare Products Regulatory Agency	UK
National Institute for Medical Research – Mbeya Medical Research Program	TZ
NNE Pharmaplan GmbH	DE
Nova Laboratories Ltd	UK

Novartis Vaccines and Diagnostics	IT
Novartis Vaccines Institute for Global Health	IT
Okairòs srl	IT
Output Pharma	DE
Pfenex Inc.	US
Preclin Biosystems AG	CH
Radboud University Nijmegen	NL
Redbiotec AG	CH
Royal College of Surgeons in Ireland	IE
Ruprecht-Karls-Universität Heidelberg	DE
Sanaria Inc.	US
Statens Serum Institut	DK
Swiss Tropical Institute	CH
TuBerculosis Vaccine Initiative	NL
Université Cheikh Anta Diop	SN
Université d'Abomey-Calavi	BN
Université Pierre et Marie Curie	FR
University of Copenhagen	DK
University of Ibadan	NI
University of Lausanne	CH
University of Lausanne (WHO reference centre)	CH
University of Maryland	US
University of Oxford	UK
Vakzine Projekt Management GmbH	DE
Vienna School of Clinical Research	AT
Voisin Consulting Life Sciences	FR
Wellcome Trust Sanger Institute	UK
World Health Organization	CH