EUROPEAN VACCINE INITIATIVE

ANNUAL REPORT 2017

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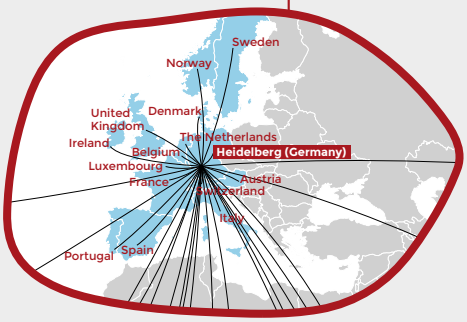


Profile

The European Vaccine Initiative (EVI) is a leading European non-profit Product Development Partnership (PDP) that is supporting global efforts to develop effective and affordable vaccines against diseases of poverty and emerging infectious diseases.

Through continuous collaborations and exchange with academia, industry, other PDPs, policy makers and donors, EVI is building a vaccine portfolio that addresses critical challenges to research and development (R&D) of vaccines for global health. EVI also engages in initiatives aimed at creating harmonisation between global stakeholders in vaccine R&D and supports capacity strengthening activities.

EVI is governed by a Board that is supported by a Board of Stakeholders (BoS) and a Scientific Advisory Committee (SAC) of international scientific experts. The EVI Secretariat is based in Heidelberg, Germany.

FOREWORD

Broadening EVI's scope

Clemens Kocken
Chairman of the European Vaccine Initiative (EVI) – European Economic Interest Grouping (EEIG)

I am delighted to share with you the EVI Annual Report 2017 and would like to highlight some of the achievements we obtained with our partners during this busy year.

EVI succeeded to secure follow-up funding for the next stage of the establishment of a sustainable European vaccine R&D infrastructure. The infrastructure has already started to offer cutting edge scientific-technical services to support innovation for the development of effective vaccines. The establishment of such an infrastructure in a sustainable manner in the long term would provide a platform to facilitate the rapid and efficient development of novel vaccines addressing global health challenges.

EVI entered a new disease area with the launch of a project related to the preclinical testing and preparation of a clinical trial of an innovative leishmaniasis vaccine. Moreover, a second project surrounding the clinical testing of another leishmaniasis vaccine is currently under negotiation and is expected to start in mid-2018

Major milestones were reached for several malaria vaccines from EVI's product portfolio. Results of a phase Ib clinical trial of the BK-SE36 malaria blood stage vaccine candidate in cohorts of malaria exposed African children are currently being analysed, the preliminary data indicate that the vaccine is safe and well tolerated. Moreover, the antibody titres increased after each immunisation and the increase was more pronounced in the younger population.

Proof-of-concept was obtained for highly effective multi-stage malaria vaccines, including first-in-human phase I clinical trials successfully completed for the sporozoite-stage malaria vaccine candidate R21, the blood-stage antigen PfRH5 and the transmission blocking vaccine candidate Pfs25. All approaches have shown favourable safety and immunogenicity profiles and important positive efficacy data were achieved in 2017 with the new R21 vaccine candidate.

The R21 malaria vaccine candidate adjuvanted with Matrix M was also administered for the first time in Africa and shown to be immunogenic in semi-immune adults with a good safety profile, results which are highly supportive for the further development of this malaria vaccine candidate. Additionally, a phase I clinical trial indicated that malaria vectored prime-boost vaccines co-administered with routine childhood immunizations were well tolerated and do not reduce the immunogenicity of co-administered other vaccines from the Expanded Programme on Immunization (EPI), supporting further evaluation of this regimen in infant populations.

Moreover, preliminary data from phase Ia/b clinical trials in Europe and Africa of the placental malaria vaccine candidates in EVI's portfolio show that both vaccine candidates are well tolerated.

Last but not least, an ambitious public-private partnership led by EVI that aims to develop and validate quality testing approaches for both human and veterinary vaccines using non-animal methods has obtained its first important achievements in the development of physiochemical, immunochemical, cell-based and other assays. Ultimately, the consortium aims to develop tests and approaches that will allow acceptance of this "consistency approach" by the regulatory agencies, thereby significantly reducing the use of animals for batch testing in routine vaccine production in the future.

The year 2018 will mark EVI's 20th anniversary! We hope you will join us in celebrating this exciting event.

GOVERNANCE

EVI BOARDS

Members of EVI Board as of 31 December 2017

The EVI Board is the ultimate and exclusive decision making body of the European Economic Interest Grouping (EEIG). In accordance with Article 8. of the Statutes, it acts collectively and the full Members are jointly and severally liable for the actions of the EEIG.

Clemens Kocken
(Chair) Chairman of the Department of Parasitology, Biomedical Primate Research Centre, Rijswijk, The Netherlands

Marita Troye-Blomberg
(Vice-Chair) Emeritus Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Sweden

Corine Kruiswijk
Institute for Translational Vaccinology, The Netherlands

Claude Leclerc
Head of Immune Regulation and Vaccinology Unit, Institut Pasteur, Paris, France

Samuel McConkey
Head of International Health & Tropical Medicine. Royal College of Surgeons., Republic of Ireland

David Salisbury
Chair of Jenner Vaccine Foundation, Oxford, United Kingdom

Wolfgang Herzog
Dean of the University Clinical Centre, Heidelberg, Germany

Martin Trillsch
Substitute for Wolfgang Herzog, Legal Council, University Clinical Centre, Heidelberg, Germany

Members of EVI Board of Stakeholders as of 31 December 2017

The EVI Board of Stakeholders consists of EVI donors and stakeholders from vaccine development and low income populations.

Sodiomon Bienvenu Sirima
(Chair) Centre National de Recherche et de Formation sur le Paludisme, Ouagadougou, Burkina Faso

Suresh Jadhav
Serum Institute of India, Pune, India

Diarmuid O'Donovan
(Vice-Chair) Service Executive, Representative of Irish Aid, Republic of Ireland

Jean-Paul H. Prieels
Chairman MaSTherCell, Brussels, Belgium

Charles de Taisne
Consultant, Retired from Sanofi Pasteur, Lyon, France

Marcel Tanner
High Ambassador, EDCTP, The Hague, The Netherlands
Retired Swiss Tropical and Public Health Institute, Basel, Switzerland

FRMC

Members of EVI Finance and Risk Management Committee (FRMC) as of 31 December 2017

The Finance and Risk Management Committee (FRMC) provides independent advice to the EVI Board on the financial reporting and on the financial risks associated with the different EVI projects. The FRMC makes recommendation to the EVI Board with regard to financial managerial decisions.

Clemens Kocken
Biomedical Primate Research Centre, Rijswijk, The Netherlands

Terry McWade
(Chair of FRMC) CEO Valitacell, Dublin, Republic of Ireland

Martin Trillsch
Legal Councel, University Clinical Centre, Heidelberg, Germany

EVI SAC

Members of EVI SAC as of 31 December 2017

The independent Scientific Advisory Committee (SAC) makes recommendations to the EVI Board on scientific direction and technologies as well as on the choice of applications for funding. The EVI SAC consists of experts in infectious diseases, immunology, regulatory and vaccine research and development.

James Searl Robertson
Independent, United Kingdom, SAC Chairperson

Michael Lanzer
UniversitätsKlinikum Heidelberg, Germany, SAC Vice-Chairperson

Giuseppe Del Giudice
Translational Science Leader, GSK Vaccines Srl, Italy

Joachim Hombach
Senior Health Adviser, Executive Secretary SAGE, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland

Nancy Le Cam Bouveret
Consultant, Canada

Dominique Mazier
Université Pierre et Marie Curie, France

SECRETARIAT

Members of EVI Secretariat as of 31 December 2017

Odile Leroy
Executive Director

Sten Larsen Finnsson
Finance and Human Resources Director

Thorsten Kohaut
Chief Finance Manager

Sophie Houard
Vaccine Development Leader

Hilde Depraetere
Senior Project Manager

Flavia D'Alessio
Project Manager

Nicola Viebig
Leader Strategic Research

Stefan Jungbluth
Head of Business Development

Oliver A. Schraidt
Project Manager

Sandra Hauenstein
Accounting Assistant

Nicolas Havelange
Production Director, Consultant

2017 GOVERNANCE EVENTS

EVI Scientific Advisory Committee (SAC)
Two EVI SAC review meetings were held by telephone conference:

- For the review of selected projects on **17 February**.
- For the annual review of EVI portfolio on **11 December**.

Mahamadou A. Thera and Ingileif Jónsdóttir completed their SAC membership terms according to the "Rules of Procedure of EVI SAC" after two three year terms of dedicated contribution to EVI. Chetan Chitnis left the EVI SAC in January. The SAC nomination committee consisting of Clemens Kocken, David Salisbury, Suresh Jadhav, James Robertson, Nancy Le Cam Bouveret and Joachim Hombach shortlisted additional potential SAC members during a telephone conference on 16 November.

EVI Board and EVI Board of Stakeholders
Three meetings for both EVI Board and Stakeholders, were held during 2017 to review the recommendations of the FRMC, strategy, advocacy, fundraising and projects.

EVI Finance and Risk Management Committee (FRMC)

The FRMC had four teleconferences to review the annual workplan, the financial audit reports and the risk register.

EDCTP/TDR Clinical research and development fellowships

The strengthening of public health and vaccine research capacities in Low- and Middle-Income Countries (LMICs) is part of EVI's mission to combat diseases of poverty. The training of scientists is key in the empowerment of research institutions in LIMCs, to address public health challenges and develop and implement appropriate solutions. EVI joined the EDCTP/TDR Clinical Research and Development Fellowship Scheme in 2016 as a hosting institution providing training to researchers from LMICs who are involved in clinical research projects. In 2017, EVI hosted two young researchers María del Mar Castro Noriega (CIDEIM, Cali, Colombia) and Siaka Débé (CNRFP, Ouagadougou, Burkina Faso).

FELLOW'S PROFILES AND THEIR EXPERIENCE AT EVI

María del Mar Castro Noriega

María del Mar started her fellowship at EVI on 9th January 2017. A native of Colombia, María del Mar is a medical doctor and MSc in Epidemiology. She works as a Clinical Investigator at CIDEIM, a Colombian non-profit institution of Biomedical Research and Training, since 2012.

Trained in both good health research practice (GHRP) and good clinical practice (GCP), she has participated in several research studies ranging from translational and epidemiological research to clinical trials, all aimed to improve management of patients with Cutaneous Leishmaniasis (CL) in Colombia.

After completion of her EDCTP/TDR Clinical Research and Development fellowship at EVI, María del Mar returned to CIDEIM as Clinical Investigator, where she is coordinating clinical research projects for CL.

"The fellowship at EVI has been an excellent experience. I have learned critical aspects of product development, especially for pre-clinical and early clinical phases. Interaction with sponsors, funders and clinical trials teams that were part of my training gave me greater understanding of clinical development questions from a strategic and sponsor's perspective. The commitment of my mentors and the support of the EVI staff made this year full of meaningful experiences, both professional and personally.

The program centred on my needs and was flexible enough to allow continuing working on certain activities of my home institution, which facilitated my reintegration to CIDEIM. As part of my re-entry, I am implementing a Project Management strategy to improve tracking of study progress in my home institution."

Siaka Débé

Siaka started his fellowship at EVI in November 2016. Siaka received a Medical Doctorate from the University of Ouagadougou in 2010. Siaka has joined CNRFP the same year where he acted as a clinical trial physician and since 2013, was in charge of the Clinical Trial Center of Balonghin. His responsibilities focused on managing the clinical trials centre, training study teams, conducting clinical trials on malaria drugs and vaccines.

In 2016, Siaka was granted a WHO/TDR clinical research development fellowship (CRDF) and was placed within EVI for a 12 months training period.

Through this placement, EVI has provided Siaka training in project management and allowed him to reinforce his network and to work in multicultural settings.

"Thanks to the EVI staff for its strong commitment in this training. I would also like to greatly thank WHO/TDR for giving me this training opportunity. This "learning by doing" approach has provided practical competencies in clinical trial development. These competencies will be profitable in my daily work and also to my home institution."

FUNDRAISING

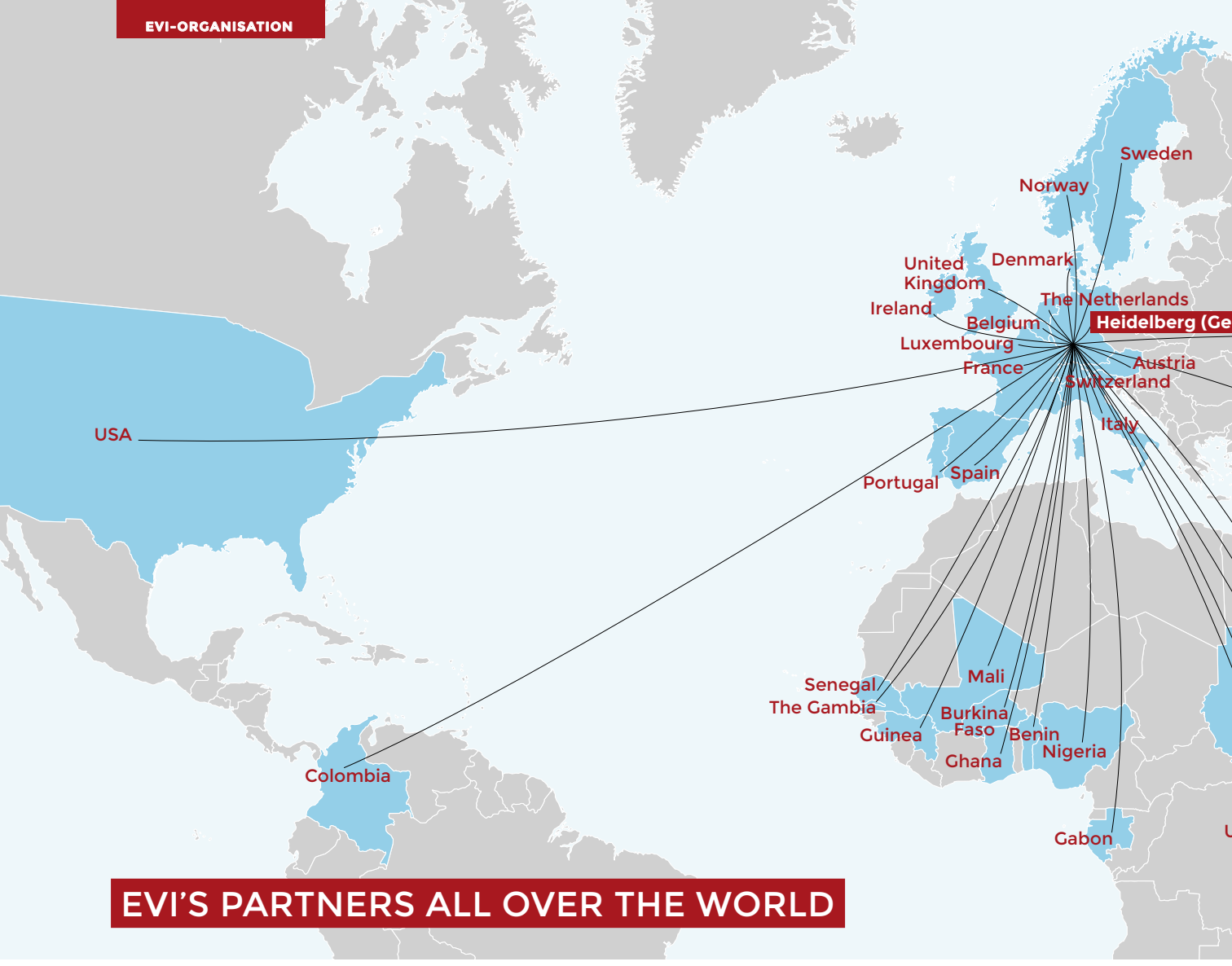
Throughout the year EVI remained extremely active in its resource mobilisation activities. In addition to new funding that could be secured thanks to these efforts, additional proposals submitted to different donors are currently pending and outcome decisions are expected for early 2018. All in all, EVI´s fundraising efforts allowed to raise the total amount of € 14,248,540 in 2017 (counting signed and implemented contracts only).

The funding secured will enable EVI to continue its long-standing efforts to establish a sustainable vaccine R&D infrastructure in the context of the EC-supported TRANSVAC2 programme, a continuation of the previous, successful TRANSVAC project led by EVI. Total EC funding to TRANSVAC2 will amount €10,599,933 for the project´s five year duration.

EVI is also proud that fresh funding was awarded by the GHIT Fund, a further demonstration of the GHIT Fund´s commitment to support EVI. The new project supported with a total funding of ¥409,666,429 or €3,148,607 relates to the further development of an innovative Leishmaniasis vaccine. This new funding therefore has allowed EVI to broaden the disease scope by including an additional neglected tropical disease in our portfolio.

Irish Aid provided EVI with core support of €500,000 which was used across many EVI activities.

EVI would like to mention the continuously on-going support of SAP. EVI has very much enjoyed the cooperation with SAP through its reference program and the joint effort for marketing and communication.



EVI'S PARTNERS ALL OVER THE WORLD

Austria
- Themis Bio
- Austrian Agency for Health and Food Safety
- Vienna School of Clinical Research

Belgium
- GlaxoSmithKline
- Novasep (formerly Henogen)
- Vaccines Europe/ European Federation of Pharmaceutical Industries and Associations
- Gent University
- Zoetis Belgium SA
- European Commission, Joint Research Centre
- Scientific Institute of Public Health
- Pro-Pay NV

Benin
- Institut de recherche clinique du Bénin
- Université d'Abomey-Calavi

Burkina Faso
- Centre national de recherche et de formation sur le paludisme
- Institut de Recherche en Sciences de la Santé
- Centre de Recherche en Santé de Nouna

Colombia
- Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM)

Denmark
- CMC Biologics A/S
- ExpreS2ion Biotechnologies A/S
- University of Copenhagen
- Bluegarden A/S
- Webland Holding ApS
- Statens Serum Institute

Ethiopia
- University of Gondor

France
- Sanofi Pasteur
- Institut Pasteur, Paris
- BIOTEM
- CiToxLAB
- Confarma
- GTP Technology
- Imaxio SA
- Agence nationale de recherches sur le sida et les hépatites virales
- Centre d'investigation clinique Cochin-Pasteur
- Commissariat à l'énergie atomique et aux énergies alternatives
- Institut de recherche pour le développement
- Institut national de la santé et de la recherche médicale
- Université Pierre et Marie Curie
- Creapharm
- QUINTEN
- Vaxyn
- Voisin Consulting Life Sciences
- Merial SAS
- Association Internationale de Standardisation Biologique pour l'Europe
- Institut Pasteur, Lille
- European Clinical Research Infrastructure Network
- Bioaster
- Institut national de la recherche agronomique

Gabon
- Centre de recherches médicales de Lambaréné
- Fondation internationale de l'hôpital du Dr Albert Schweitzer de Lambaréné
- Albert Schweitzer Hospital

Germany
- Paul-Ehrlich-Institut
- IDT Biologika
- NNE Pharmaplan GmbH
- Output Pharma
- Eberhard-Karls Universität Tübingen
- Fraunhofer IME
- Ludwig-Maximilians-Universitaet München
- Boehringer Ingelheim Vetmedica GmbH
- Mologen AG
- SAP SE
- All4Cloud GmbH
- Falk & Co GmbH
- BDO AWT GmbH
- Charité – Universitätsmedizin
- Helmholtz Centre for Infection Research
- Heidelberg University

Ghana
- Kintampo Health Research Centre

India
- Zydus Cadilla
- DiagnoSearch Life Sciences Pvt. Ltd.
- International Centre for Genetic Engineering and Biotechnology

Ireland
- Royal College of Surgeons

Italy
- Istituto Superiore di Sanità
- ETNA Biotech s.r.l.
- Novartis
- Novartis Vaccines Institute for Global Health
- ReiThera s.r.l. (formerly Okairòs s.r.l.)
- Sclavo Foundation
- University of Siena
- Novartis Vaccines and Diagnostics s.r.l.
- Instruct

Japan
- Nobelpharma
- Research Institute for Microbial Diseases
- Institute of Tropical Medicine Nagasaki University
- Institute of Tropical Medicine (NEKKEN), Nagasaki University

Kenya
- Kenya Medical Research Institute

Luxembourg
- TGC Luxembourg Sàrl

Mali
- Malaria Research and Training Centre

Nigeria
- University of Ibadan

Norway
- University of Bergen

Portugal
- Instituto de Biologia Experimental e Tecnológica
- Genibet

Senegal
- Pharmalys
- Université Cheikh Anta Diop

Spain
- Institute of Agrifood Research and Technology

Sudan
- University of Khartoum

Sweden
- Stockholm University
- AstraZeneca AB
- Novavax (formerly ISCONOVA)

Switzerland
- Preclin Biosystems AG
- Redbiotec AG
- Developing Countries Vaccine Manufacturers Network
- Malaria Vaccine Funders Group
- Roll Back Malaria
- World Health Organization
- Centre hospitalier universitaire Vaudois
- École polytechnique fédérale de Lausanne
- Swiss Tropical and Public Health Institute
- University of Lausanne
- ETH Zurich

Tanzania
- Ifakara Health Institute
- National Institute for Medical Research – Mbeya Medical Research Program

The Gambia
- Medical Research Council Gambia

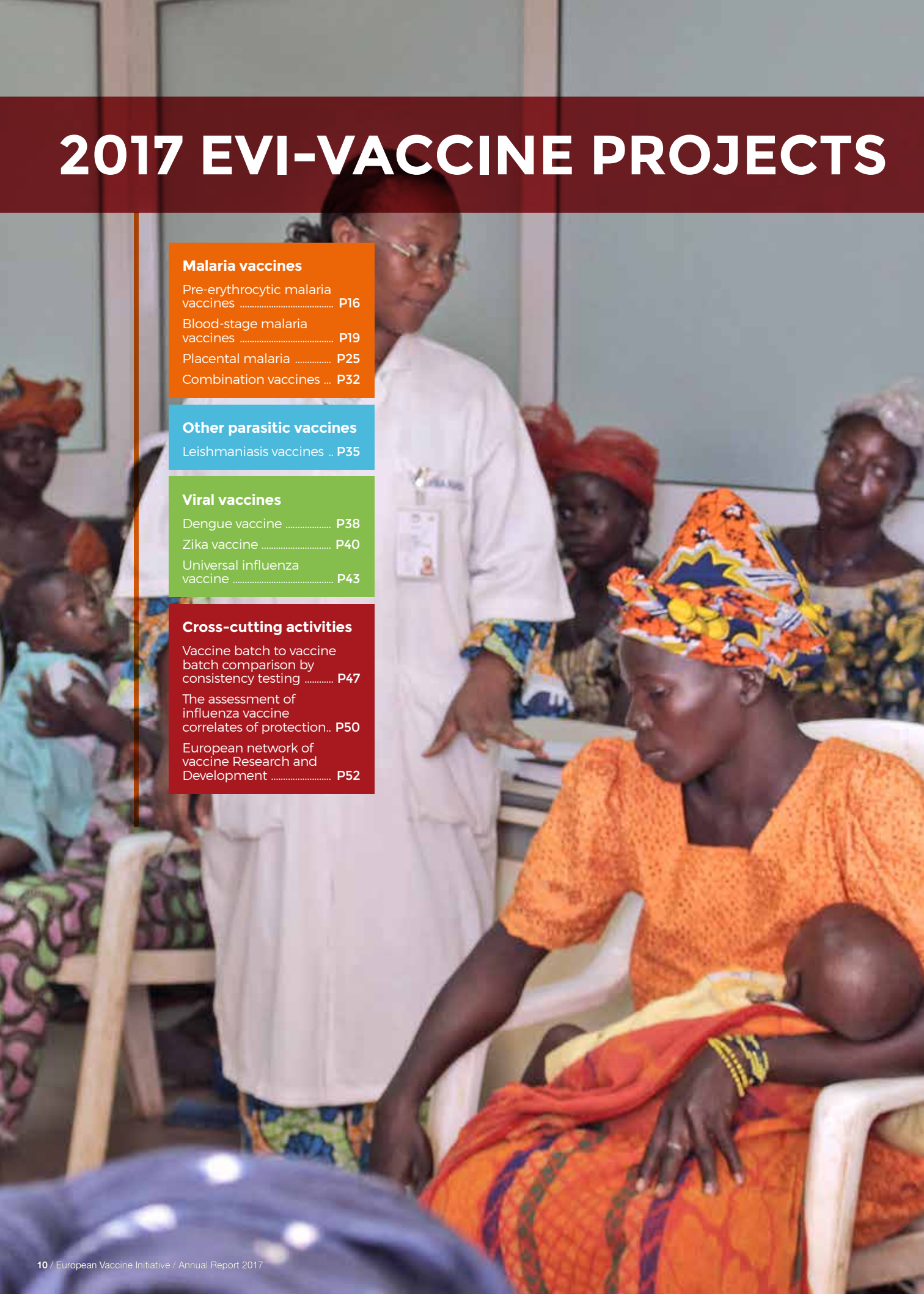
The Netherlands
- Erasmus University Medical Centre Rotterdam
- Biomedical Primate Research Centre
- Institute for Translational Vaccinology
- Abbott
- Artemis One Health Research BV
- Janssen
- European Advanced Translational Research Infrastructure in Medicine
- Academisch Medisch Centrum bij de Universiteit van Amsterdam
- Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum
- Wageningen Bioveterinary Research
- Intervet International BV (MSD)
- National Institute for Public Health and the Environment/ Rijksinstituut voor Volksgezondheid en Milieu
- University Medical Center Groningen
- University of Applied Sciences Utrecht
- University of Utrecht
- Wageningen University and Research Centre
- University of Leiden

Uganda
- Medical Research Council Uganda on behalf of its MRC/UVRI Uganda Research Unit on AIDS
- Uganda Virus Research Institute
- Makerere University

United Kingdom
- Pharmalys
- National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare Products Regulatory Agency
- Jenner Vaccine Foundation
- ALMAC Sciences
- Nova Laboratories Ltd
- European Medicines Agency
- Jenner Institute
- London School of Hygiene and Tropical Medicine
- MHRA-Department of Health
- University of Oxford
- Wellcome Trust Sanger Institute
- Prentis & Co Ltd
- Vaccine Formulation Institute

USA
- Pfenex Inc.
- Infectious Diseases Research Institute
- National Institute of Health/National Institute of Allergy and Infectious Diseases
- PATH Malaria Vaccine Initiative

2017 EVI-VACCINE PROJECTS



STRENGTHENING THE PORTFOLIO

	DISCOVERY	PRE-CLINICAL PROOF OF CONCEPT	CLINICAL PROOF OF CONCEPT			DEVELOPMENT	ACCESS
	DISCOVERY	PRE-CLINICAL	PHASE Ia	PHASE Ib	PHASE IIa	PHASE IIb/III	POST-APPROVAL
MALARIA			R21 (AS01)	R21 (Matrix M1)	R21/Matrix M1 ME-TRAP ChAd63/MVA	R21 (AS01)	
			CSVAC ChAd63/MVA				
			RH5			GMZ2 GLURP+MSP3	
			RH5 ChAd63/MVA			MSP3	
			BK-SE36 CpG	BK-SE36	BK-SE36		
			AMA1-Dico				
			P27A				
			PRIMVAC VAR2CSA				
			PAMVAC VAR2CSA				
			Pfs25 – IMX313 ChAd63/MVA				
LEISHMANIASIS		LEISHDNAVAX					
DENGUE	15 constructs of EDIII-ectoM and NS1	MVDVax					
ZIKA	± 40 constructs screened	MV-Zika					
INFLUENZA	Up to 15 HAs, 6 Group 2 HAs & 3NA sequences	EDUFLUVAC VLP					
CROSS-CUTTING		VAC2VAC					
		FLUCOP					
		TRANSVAC2					

● Malaria pre-erythrocytic ● Malaria blood-stage ● Malaria transmission-blocking

MALARIA VACCINES

Blood-stage malaria vaccines: AMA1-DiCo, P27A, BK-SE36 and PfRH5

The age-de-escalation phase Ib clinical trial of BK-SE36 vaccine candidate commenced with the immunisation of children aged 2–5 years old and, following safety data review, it expanded to include the younger population aged 1–2 years old. The last boost immunisation was administered in April 2016, the trial follow-up phase ended in February 2017. Safety data and IgG titres collected until one month after the last immunisation indicate that the BK-SE36 vaccine is safe, well tolerated and immunogenic. The BK-SE36/CpG phase Ib trial received favourable opinion from the national ethics committee of Burkina Faso and by the UK and Japanese ethics committee in November 2017.

The PfRH5 antigen expressed in viral vectors was assessed using a heterologous prime-boost regime (ChAd63 followed by MVA) in a phase Ia clinical trial in the UK. The vaccine candidate achieved a good safety and immunogenicity profile, including functional antibodies detected in *in vitro* assays. PfRH5 is the first antigen to induce substantial cross-strain GIA following viral vectored vaccination in a clinical trial. A manuscript was published in JCI Insight in November 2017.

The EVI fast-track strategy for early clinical development in Europe and Africa was successful for both the AMA1-DiCo and P27A vaccines, and the phase Ia/b clinical trials were completed in France/Burkina Faso and Switzerland/Tanzania, respectively. The safety and immunogenicity analysis indicate that both vaccine candidates are safe, well tolerated and immunogenic in malaria naïve and exposed population. The AMAI-DiCo clinical trial phase Ia/Ib results of the primary and secondary objectives were published.

Placental malaria vaccines: PAMVAC, PRIMVAC

The development of placental malaria vaccines by three major research groups led by Thor Theander and Morten Nielsen in Denmark, Benoit Gamain in France, and Patrick Duffy in the USA remains a major focus of EVI. In Denmark, the PAMCPH/PlacMalvac project completed a phase Ia/b clinical trial assessing the safety and immunogenicity of the placental malaria vaccine candidate PAMVAC adjuvanted with Alhydrogel, GLA-SE and GLA-LSQ in Germany and Benin. The PRIMALVAC phase Ia/b clinical trial assessing the vaccine candidate PRIMVAC adjuvanted with Alhydrogel or GLA-SE in France and Burkina Faso completed the one year follow-up period for the phase Ia arm in France and fully enrolled and completed vaccinations in the phase Ib arm in Burkina Faso. To accelerate the decision process for assessment and the selection of placental malaria antigens, EVI is supporting the PlacID project for the development of a non-human primate model for placental malaria at NIH/NIAID in the USA.

Pre-erythrocytic malaria antigens: ME-TRAP, R21

Within MVVC 2, good safety and immunogenicity profiles were achieved for Matrix-M1 adjuvanted R21 in a phase Ib clinical trial in healthy African adults at the CNRFP, Burkina Faso. Further analyses confirmed the good safety and immunogenicity results of the viral-vectored ME-TRAP vaccine candidate co-administered with the Expanded Programme on Immunization (EPI) vaccines in the MVVC 2 phase Ib clinical trial in The Gambia. The study was published in Frontiers in Immunology.

MultiMalVax successfully completed first-in-human phase I clinical trials for the adjuvanted sporozoite-stage malaria vaccine candidate R21, the blood-stage antigen PfRH5 and the transmission blocking vaccine candidate Pfs25, to complement the already available ME-TRAP vectored liver-stage vaccine candidates. This was completed by combination phase I/II clinical trials assessing GSK's RTS,S administered with vectored ME-TRAP as well as R21 in adjuvant administered with or without vectored ME-TRAP. All approaches have shown favourable safety and immunogenicity profiles and important positive efficacy data was achieved in 2017 with a new vaccine candidate. Progress was also made in the establishment of a functional *in vitro* assay that allows quantification and further analyses of the immunological responses induced by liver-stage vaccines.

Transmission-blocking vaccine: Pfs25

The transmission-blocking vaccine candidate Pfs25 is expressed using the viral vectors ChAd63/MVA in which the antigen is fused to the IMX313 fusion tag. IMX313 promotes the oligomerisation of the antigen and potentially increases both B cell and T cell immunogenicity. This strategy is expected to improve the efficacy of the vaccine candidate. The phase I clinical trial in healthy volunteers aged 18–50 began in 2015 and indicated that the vaccines have been well tolerated and induced antigen-specific T cell as well as antibody responses after vaccination.

LEISHMANIASIS VACCINES

LEISHDNAVAX

In October 2017 EVI and its partners from Nagasaki University, Mologen AG, Charité – Universitätsmedizin Berlin and the London School of Hygiene and Tropical Medicine (LSHTM) have been awarded GHIT funds to support the preclinical evaluation of a novel leishmaniasis DNA vaccine candidate and for preparing the conduct of a future Phase I clinical trial. LEISHDNAVAX is a DNA vaccine candidate that has been successfully tested for antigenicity in humans in *ex vivo* studies, and for

efficacy in a mouse model for visceral leishmaniasis. The main objective of the proposed project is to complete the preclinical development to assess its prophylactic and therapeutic effect against cutaneous leishmaniasis.

VIRAL VACCINES

ZIKAVAX

With the recent outbreak of Zika virus infections, EVI and partners embarked in October 2016 on the development of a safe and effective preventive vaccine against Zika virus infection. The vaccine concept is based on the use of the measles vector (MV) as a delivery platform technology for the Zika antigen(s). Preclinical studies were conducted in order to down-select the vaccine candidates that were subsequently evaluated for immunogenicity and efficacy in the mouse model. Additionally, a non-human primate (NHP) challenge model for Zika virus infection was established at CEA that will be used to assess the best performing MV-Zika vaccine candidates in 2018.

EDUFLUVAC

After four years of collaborative research activities towards the development of a broadly reactive influenza vaccine, the EDUFLUVAC project was concluded in October 2017. The consortium partners successfully completed the proof of concept challenge studies in ferrets and non-human primates with the vaccine candidate(s) selected, based on the mouse immunogenicity results. A third and last workshop was organised by the project partners in Brussels on 12-13 June 2017. The workshop entitled: "Four years of European research on the development of universal influenza vaccines: what have we learnt and how can we move forward?" brought together representatives from the five EU-funded consortia aiming at developing broadly reactive influenza vaccines to discuss the products and technologies developed and how to strengthen the European vaccine development landscape.

MVDVax

EVI supported the development of a dengue vaccine based on the MV delivery platform. An optimised immunisation protocol was developed for NHP vaccination. The dengue antigens expressed in the attenuated measles virus vectors (MVDVax) induced promising antibody titres in the NHP vaccinations, and reduced viremia upon challenge, but did not protect from Dengue virus infection.

CROSS-CUTTING ACTIVITIES

VAC2VAC

The overall objective of the "Vaccine batch to vaccine batch comparison by consistency testing" project (acronym: VAC2VAC) is to demonstrate the proof of concept of the consistency approach for batch release testing of established vaccines. Sets of *in vitro* assays are to be used to ensure that each vaccine batch from an individual manufacturer is consistent with a batch already proven to be safe and efficacious in registration studies, thus ensuring consistent quality of the vaccine released to market.

FLUCOP

FLUCOP aims to improve and standardise existing immunological assays for influenza vaccines, assays that would be of great use for the identification of correlates of protection in future vaccine efficacy trials. Moreover, within this project –that is supported by IMI and EFPIA– efforts are undertaken to develop new assays for a better assessment of the immunogenicity of influenza vaccines. In 2017, major progress was made concerning the development of standardised hemagglutination-inhibition assays (HAI) and towards the establishment of a peripheral blood mononuclear cells (PBMC) biobank, ultimately to be used for the standardisation and evaluation of assays to measure influenza-specific cell-mediated immunity.

TRANSVAC

The overall objective of TRANSVAC2 is to support innovation for both prophylactic and therapeutic vaccine development. The infrastructure is based on a collaborative one-health approach with a coordinated set of efforts focusing on multiple disciplines and diseases (working locally, nationally, and globally) with the goal of attaining freedom from infectious diseases for both people and animals. TRANSVAC2 aims to optimise the existing knowledge and expertise gained during the development of human and animal vaccines by supporting the translational gap in biomedical research, and by establishing mutually-beneficial cooperation between public vaccine R&D institutions, vaccine initiatives and networks, related infrastructures, SME's, and partners in the pharmaceutical industry.

Malaria vaccines

Malaria is a mosquito-borne disease caused by protozoan parasites of the genus *Plasmodium*. Malaria causes symptoms that typically include fever, chills, tiredness, vomiting, and headaches. Left untreated, patients may develop severe complications and die. Life-threatening complications may include e.g. pulmonary oedema leading to breathing difficulties, kidney failure, abnormal liver function leading to jaundice and liver failure, aplastic anaemia and severe infection of the brain (cerebral malaria), with seizures, confusion, and increasing tiredness leading to coma and death. Symptoms usually begin ten to fifteen days after being bitten by an infected female Anopheles mosquito. Immunity to *P. falciparum* malaria only develops slowly and only leads to partial and short lived immunity in response to repeated infections.

Epidemiology and disease burden

Despite intensive control efforts over the past decade, malaria remains one of the most significant global public health problems. There were 216 million reported cases of malaria worldwide (95% CI: 196–263 million) compared with 237 million cases in 2010 (95% CI: 218–278 million) leading to 445,000 deaths globally, of which 407,000 deaths (approximately 91%) were in the WHO African Region[1]. From the *Plasmodium* species, *P. falciparum* is responsible for the majority of severe malaria cases and deaths. Mortality occurs primarily in infants and young children in sub-Saharan Africa, although pregnant women are also affected with severe potential impact on the developing foetus.

Control measures & prevention

Current efforts to control malaria rely on the use of insecticide treated bed nets and indoor residual spraying of houses to limit human contact with vectors, combined with early detection and treatment of malaria patients, currently with artemisinin combination therapy. Intensive implementation of these malaria control measures over the past couple of decades has led to significant reduction in transmission rates and malaria incidence. However, these measures are resource-intensive and need to be applied continuously, which raises questions of long-term sustainability, especially in resource-poor countries where malaria is endemic. Moreover, the rise and spread of artemisinin resistant *P. falciparum* strains threatens the efficacy of the current mainstay of malaria therapy[2]. While other antimalarial drugs are in development, *P. falciparum* parasites have become resistant to every drug put into widespread use so far, emphasising that drug treatment alone is not a viable elimination strategy.

Therefore, the development of vaccines targeting *P. falciparum* malaria would provide an extremely valuable, cost-effective tool complementary to current malaria control methods, and could add significantly to efforts to the eliminate and ultimately eradicate malaria.

Vaccine landscape

The Malaria Vaccine Technology Roadmap[3] set the strategic goal to licence vaccines targeting *P. falciparum* and *P. vivax* that encompass the following two objectives:

- Development of malaria vaccines with protective efficacy of at least 75% against clinical malaria suitable for administration to appropriate at-risk groups in malaria-endemic areas.
- Development of malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection.

The vaccine candidates currently under development target different parasite stages within the malaria life-cycle. Vaccine candidates are directed against the pre-erythrocytic stages including sporozoites and liver-stages, and the blood-stages that are replicating within the erythrocytes, in addition to vaccine candidates that target antigens on sexual stages, the so called transmission-blocking vaccines. Despite a large number of malaria vaccines in clinical development over the last decades, the highly polymorphic nature of many *P. falciparum* proteins results in significant challenges to vaccine design. The most advanced malaria vaccine is GSK's RTS,S pre-erythrocytic vaccine that is entering pilot implementation studies in 2018.

1. World Health Organization, "World Malaria Report 2017", (2017).
2. F. Ariey *et al.*, A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. Nature 505, 50-55 (2014).
3. Malaria Vaccine Technology Roadmap (2013): http://www.who.int/immunization/topics/malaria/vaccine_roadmap/TRM_update_nov13.pdf?ua=1

VACCINES THAT PREVENT MALARIA INFECTION:

Pre-erythrocytic malaria vaccines

Malaria vaccines targeting the pre-erythrocytic stages are designed to prevent sprorozoite invasion of hepatocytes and to impede the development of the parasite inside the hepatocytes, thereby preventing the development of the parasite into symptomatic blood-stages. Two main effector mechanisms are targeted to protect from malaria: antibodies that neutralise extracellular sporozoites by targeting surface exposed antigens, and T cells that eliminate intracellular liver stages after recognition of parasite-derived peptides presented to the immune cells on the hepatocyte surface.

Vaccine development has been a focus of malaria research for decades, but the majority of efforts have focussed on only a handful of pre-erythrocytic candidates. The RTS,S vaccine (Mosquirix™) developed jointly by the Malaria Vaccine Initiative (MVI PATH) and GSK is the only recombinant malaria vaccine to reach phase III clinical trials. However, the efficacy of RTS,S adjuvanted with AS01 is rather modest (39%)[4], it achieves relatively short-term protection, and a series of four vaccinations is required. To assess the vaccine's protective effect in real-life settings, the RTS,S vaccine will be rolled out in pilot implementation projects in three sub-Saharan Africa countries with start of vaccinations in 2018. Another approach, which has provided some evidence for significant efficacy is immunisation with irradiated sporozoites. Although this approach elicits significant protective efficacy against challenge with the homologous *P. falciparum* strain[5], attempts to increase the efficacy against heterologous strains and the duration of protection are underway. New approaches leading to a second-generation malaria vaccine are urgently needed.
The EVI portfolio currently includes leading pre-erythrocytic malaria vaccine programs. The first programme is based on the RTS,S biosimilar R21 that is expected to elicit an improved malaria-specific immune response. The second approach uses the viral vectored prime-boost strategy where the modified vaccinia Ankara virus (MVA) is used for priming and a chimpanzee adenovirus (ChAd63) is used for boosting immune responses against the ME-TRAP antigen.

MVVC 2

The EVI coordinated MVVC 2 project built on the MVVC project which established a strong network among four African partners and the collaborators in Europe. This network was enlarged to include two new partners, and capacity-strengthening efforts were expanded during the course of MVVC 2.

The three-year MVVC 2 project (2012-2015) was 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 was complemented by co-funding from EU Member States:

- Bundesministerium für Bildung und Foschung (BMBF), Germany,
- Irish Aid, Department of Foreign Affairs and Trade, Ireland,
- Medical Research Council (MRC), UK,
- Swedish Development Agency (Sida), Sweden,

and third-party contributions, with a total project budget of approximately €1,2m.

4. The RTS,S Clinical Trials Partnership (2014). PLoS Medicine 2014, doi.org/10.1371/journal.pmed.1001685
5. R. A. Seder *et al.*,. Science 341, 1359-1365 (2013).

PARTNERS

- Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso
- European Vaccine Initiative (EVI), Germany
- Kenya Medical Research Institute (KEMRI), Kenya
- Kintampo Health Research Centre (KHRC), Ghana
- Medical Research Council (MRC), Gambia
- Novartis Vaccines and Diagnostics, Italy
- ReiThera s.r.l., IT (formerly Okairòs s.r.l.), Italy
- Université Cheikh Anta Diop (UCAD), Senegal
- University of Oxford (UOXF), United Kingdom
- Vienna School of Clinical Research, Austria (until 31 Jan 2013)

MVVC 2 aimed to determine whether the virally vectored prime-boost malaria vaccines are compatible with the EPI vaccination schedule and whether an adjuvanted Circumsporozoite Protein (CSP) particle (R21) is safe and immunogenic. As part of the integrated strategy, workshops, training and networking activities as well as infrastructure upgrades were used to strengthen the clinical trial capabilities and laboratory facilities of the African sites, allowing the partners to conduct the proposed clinical trials and additional health research. The KHRC site also developed capacity in cellular immunology.

RECENT ACHIEVEMENTS A phase I clinical trial at MRC, The Gambia indicated that malaria vectored prime-boost vaccines co-administered with routine childhood immunisations were well tolerated. Potent humoral and cellular immunity induced by ChAd63 MVA ME-TRAP did not reduce the immunogenicity of co-administered EPI vaccines, supporting further evaluation of this regimen in infant populations. Additionally, the Matrix M adjuvanted R21 malaria vaccine candidate was administered for the first time in Africa. The vaccine was immunogenic in semi-immune adults with a good safety profile. These data are supportive for further development of the R21 malaria vaccine candidate.

MVVC2

Delivery Platform, Adjuvants and Viral Vectors

The malaria antigen ME-TRAP was delivered in a prime boost strategy using two different vectors: ChAd63 and MVA. The adjuvant used to administer the R21 CSP particles was Matrix-M1, provided by Novavax.

Clinical Development

In a first clinical trial, this project aimed to determine whether malaria-vectored prime-boost vaccines are compatible with the EPI vaccination schedule and whether a CSP particle in adjuvant is safe and immunogenic (ClinicalTrials.gov Identifier: NCT02083887). The safety and immunogenicity of the vectored liver-stage malaria vaccine candidates co-administered with EPI vaccines were assessed in Gambian infants 1–16 weeks of age at the MRC in a truly South-South collaborative clinical trial with the support of the UCAD team. The clinical trial revealed good safety and immunogenicity profiles in all infant age groups.

The study team enrolled 65 Gambian infants and neonates priming at sixteen, eight or one week of age, and randomized them to receive either ME-TRAP and EPI vaccines or EPI vaccines only. All participants received EPI vaccines according to the national programme. Safety was assessed by the description of vaccine-related adverse events including clinical assessments, biochemical and haematological tests. Immunogenicity was evaluated using anti-TRAP IgG ELISA, interferon-gamma ELISpot and whole blood flow cytometry. Serology was performed to confirm all infants achieved protective titres to EPI vaccines.

The vaccines were well tolerated in all age groups with no vaccine-related serious adverse events. High-level TRAP specific IgG and T cell responses were generated after boosting with MVA. Particularly, CD8+ T cell responses, previously found to correlate with protection, were induced in all age groups. Antibody responses to EPI vaccines were not altered significantly.

While difficult to induce in neonates with protein or polysaccharide vaccines, potent humoral and cellular immunity was generated by heterologous prime-boost immunization with ChAd63/MVA ME-TRAP in young infants and neonates. Co-administration of routine EPI vaccines did not reduce these responses. The EPI vaccines also retained protective antibody titres following administration of the malaria vaccines, supporting further evaluation of this regimen in infant populations.

The clinical trial data was published in Frontiers in Immunology in November 2017.

The second clinical trial, conducted at CNRFP, assessed the safety, reactogenicity and immunogenicity of three doses of 10µg of the malaria vaccine candidate R21 adjuvanted with Matrix-M1 in healthy West African adult volunteers living in a malaria-endemic area, in a phase Ib randomised, controlled, single-blind study (ClinicalTrials.gov Identifier: NCT02925403).

Volunteers were randomly assigned in a 2:1 ratio to receive 3 doses of the malaria vaccine or the control (normal saline) intramuscularly one month apart. Participants were actively followed up daily at home during the 7 days following each vaccination to collect local and systemic solicited adverse events. Serious adverse events were recorded throughout the study duration. Venous blood samples were obtained for clinical safety and immunological evaluations. The study duration was 140 days for each participant.

In conclusion, this was the first administration of the R21 malaria vaccine candidate in Africa. The vaccine was immunogenic in semi immune adults with a good safety profile. These data are supportive for further development of the R21 malaria vaccine candidate.

A manuscript is in preparation.

Capacity strengthening, Workshops, Training

As part of the MVVC 2 capacity-strengthening activities, immunology facilities at the KHRC, Ghana, have been secured and made available. The laboratory facilities have been established, equipment has been sourced and personnel trained.

Exchange visits took place within the project duration to reinforce collaborations, especially between the African project partners. A true example of South-South collaboration was the exchange of expertise and laboratory personnel between the UCAD, Senegal and the MRC, The Gambia. The UCAD senior scientific staff gained experience by establishing and conducting paediatric malaria clinical trials while two UCAD laboratory technicians supported immunological analysis at the MRC.

The working platform offered by the MVVC 2 project has been a great opportunity for the professional growth of the staff involved in the project. Exchange visits, meetings and short-term training activities created a highly stimulating working environment and have been instrumental to the formation of very competent clinical researchers. UOXF was responsible for the quality assurance of all immunoassays performed during MVVC 2. This enabled the young scientists at the Jenner Institute laboratories to gain valuable experience in the performance of these assays from samples obtained from clinical trials conducted in malaria endemic countries.

Harmonisation

The MVVC 2 consortium has expanded the MVVC harmonisation efforts on immunoassays to include KHRC, and those concerning quantitative PCR to include CNRFP. This ensures that the sites generated comparable results in the MVVC 2 project and will generate in future clinical trials.

Outreach and Communication

Alfred B. Tiono (CNRFP) presented: "Safety and immunogenicity of the Malaria Vaccine Candidate R21 adjuvanted with Matrix-M1 in West African adult volunteers" at the 10th European Congress on Tropical Medicine and International Health, Antwerp, Belgium, 16-20 October 2017.

Alfred B. Tiono (CNRFP) presented: "Safety and immunogenicity of the Malaria Vaccine Candidate R21 adjuvanted with Matrix-M1 in West African adult volunteers" at the ASTMH 66th Annual Meeting, 05-09 November, Baltimore, USA

Sophie Roetynck (MRC) presented "Safety and immunogenicity of ChAd63/MVA ME-TRAP malaria vectored vaccine given with routine EPI vaccines in Gambian infants and neonates: a randomised controlled trial" at the 4th International Neonatal & Maternal Immunization Symposium, Brussels, Belgium, 10-12 September 2017.

The VAC058 clinical trial results were published: Mensah VA, Roetynck S, Kanteh EK, Bowyer G, Ndaw A, Oko F, Bliss CM, Jagne YJ, Cortese R, Nicosia A, Roberts R, D'Alessio F, Leroy O, Faye B, Kampmann B, Cisse B, Bojang K, Gerry S, Viebig NK, Lawrie AM, Clarke E, Imoukhuede EB, Ewer KJ, Hill AVS, Afolabi MO. Safety and Immunogenicity of Malaria Vectored Vaccines Given with Routine Expanded Program on Immunization Vaccines in Gambian Infants and Neonates: A Randomized Controlled Trial. Front Immunol. 2017 Nov 20;8:1551. doi: 10.3389/fimmu.2017.01551. eCollection 2017. PMID: 29213269

MALARIA VACCINES THAT PREVENT MORTALITY AND MORBIDITY:

blood-stage malaria vaccines

Clinical malaria occurs when *Plasmodium* parasites invade and replicate within red blood cells (the so called blood-stage infection). However, immunological studies in humans and animals have demonstrated that the immune response induced by blood-stage antigens can protect against the disease.

Blood-stage malaria vaccines aim to prevent mortality, reduce clinical disease and transmission, whilst potentially allowing for natural boosting of vaccine-induced responses as well as the acquisition of natural immunity[6]. Neutralising antibodies are most often sought that (i) prevent interactions between ligands of the invasive blood-stage merozoite and protein receptors present on the host red blood cell surface[7]; (ii) prevent the interaction of the parasite antigens displayed on the red blood cell surface with host cell receptors[8]; (iii) recognise antigens that get exposed upon parasite egress[9] and/or (iv) activate monocytes that inhibit parasite growth[10]. Indeed, passive transfer studies have shown that immunoglobulins from semi-immune individuals can confer clinical immunity to individuals exposed to geographically diverse parasite strains[11]. Studies in humans and animals have shown that controlling parasite density can reduce the generation of gametocytes in the bloodstream, thus also limiting transmission.

Blood-stage malaria vaccines represent an alternative and/or complementary approach to pre-erythrocytic vaccines and will probably be an important component of a second-generation multi-antigen, multi-stage malaria vaccine. However, the development of an effective blood-stage malaria vaccine has proved challenging. Most antigens currently used as vaccine candidates are merozoite antigens. Currently only two blood-stage vaccine candidates have been evaluated in phase II trials however with disappointing results. The 3D7 based adjuvanted apical membrane antigen 1 (AMA1) antigen FMP2.1/AS02$_A$ has demonstrated protective efficacy against clinical malaria for the homologous parasite in phase II clinical trial so far[12]. The GLURP-MSP3 based GMZ2/Alum vaccine candidate has shown very modest efficacy in the target population indicating the need of a more immunogenic formulation[13].

EVI has developed several blood-stage antigens with the intention of combining them either with pre-erythrocytic or other blood-stage antigens in a second generation of malaria vaccines. To overcome antigenic diversity in the development of blood-stage vaccines, ideally, vaccine candidates should be based on less polymorphic and more conserved antigen domains or cover the diversity. EVI's current approaches include the development of recombinant antigens (AMA1-DiCo, SE36) and synthetic peptides (P27A) as well as virally vectored antigens (PfRH5).

6. Goodman A.L. *et al.* Ann Trop Med Parasitol 2010, doi:10.1179/136485910X12647085215534.
7. Wright G.J. and Rayner J.C. PloS Pathogens 2014, doi:10.1371/journal.ppat.1003943.
8. Chan J.A. *et al.* Cell Mol Life Sci. 2014, doi:10.1007/s00018-014-1614-3.
9. Kulangara C. *et al.* PLOS ONE 2012, doi:10.1371/journal.pone.0046112.
10. Olugbile S. *et al.* Infection and Immunity 2009, doi:10.1128/IAI.00652-09.
11. Sabchareon A. *et al.* Am J Trop Med Hyg. 1991, Sep;45(3):297-308.
12. Thera M.A. *et al.* N Engl J Med. 2011, doi:10.1056/NEJMoa1008115.
13. Sirima SB *et al.* Vaccine. 2016 Aug 31;34(38):4536-4542. doi: 10.1016/j.vaccine.2016.07.041.

AMA1-DiCo

Apical Membrane Antigen 1 (AMA1) is a protein of apicomplexan parasites with an essential role in host cell invasion. The AMA1 ectodomain is an important *Plasmodium falciparum* blood-stage vaccine target and antibodies against the ectodomain have been shown to interfere with AMA1 processing and prevent red cell invasion *in vitro*.

PARTNERS

- Biomedical Primate Research Centre (BPRC), The Netherlands
- Centre d'investigation clinique Cochin-Pasteur (CIC-Cochin), France
- Centre national de recherche et de formation sur le paludisme (CNRFP), Burkina Faso
- Confarma, France
- European Vaccine Initiative (EVI), Germany
- Fraunhofer Institute for Molecular Biology and Applied Ecology (Fraunhofer IME), Germany
- Gregory Fryer Associates Ltd, United Kingdom
- Novasep (formerly Henogen), Belgium
- Infectious Diseases Research Institute (IDRI), United States of America
- Institut national de la santé et de la recherche médicale (Inserm), France
- NNE Pharmaplan GmbH, Germany
- Nova Laboratories, Ltd, United Kingdom
- Output Pharma, Germany
- WIL Research, The Netherlands

AMA1 was evaluated in a phase Ia clinical trial with three different adjuvants: Alhydrogel, AS02$_A$ and Montanide ISA720. The results were promising, however one conclusion of this clinical trial was that polymorphism in the PfAMA1 protein must be addressed for the vaccine to be highly effective in the field.

To overcome the AMA1 antigen polymorphism, the AMA1 Diversity Covering (DiCo) proteins were designed by Edmond Remarque at BPRC. To this end, three artificial protein sequences were constructed incorporating a high degree of variation based on sequences available at the time of design. Immunization with a mixture of three DiCo proteins yielded antibodies capable of inhibiting *in vitro* growth of a panel of AMA1 variants in rabbits and non-human primates.

The total budget for the development of an AMA1-DiCo vaccine is €5,411,742.23, from the Directorate General for International Cooperation at Ministry of Foreign Affairs, The Netherlands (DGIS) and Irish Aid grants.

The AMA1-DiCo vaccine was evalutated in a phase Ia/Ib clinical trial conducted in France and Burkina Faso. The trial evaluated the safety and immunogencity of three doses of 50µg AMA1-DiCo formulated with either GLA-SE or Alhydrogel® adjuvant. Following a positive safety assessment after two doses in French volunteers, GLA-SE was chosen for the phase Ib trial conducted in Burkinabe volunteers. In the African volunteers, the safety and immunogenicity of three doses of 50µg AMA1-DiCo formulated with GLA-SE were evaluated and compared to a saline control.

AMA1-DiCo was deemed safe and well tolerated either with Alhydrogel® or GLA-SE. In European volunteers, the ratios of IgG increase from baseline were about 100 fold in Alhydrogel® group and 200-300 fold in GLA-SE group for the three antigens. In African volunteers, immunisation resulted in IgG levels exceeding those observed for the European volunteers with a 4-fold increase. DiCo-specific IgG remained higher 26 weeks after the third immunization than at baseline in both European and African volunteers. Induced antibodies were reactive against whole parasite derived from different strains.

AMA1-DiCo formulated with aluminium hydroxide or GLA-SE was well tolerated and induced high titres of specific antibodies in malaria-exposed or non-exposed populations, although the titres were higher when the antigen was formulated with GLA-SE in the non-exposed population[14]. Further exploratory analysis is underway to assess the functionality of the antibodies.

RECENT ACHIEVEMENTS The main achievement in 2017 was the publication of the AMA1-DiCo clinical trial phase Ia/Ib results of the primary and secondary objectives.

14. Sirima SB, *et al.*, Vaccine. 2017 Oct 27;35(45):6218-6227. doi: 10.1016/j.vaccine.2017.09.027. Epub 2017 Sep 22.

AMA1-DiCo

Delivery Platform, Adjuvants and Viral Vectors

Glucopyranosyl Lipid A Adjuvant (GLA)-Stable Emulsion (SE) (IDRI) and aluminium hydroxide (Alhydrogel®) as a comparator have being used as adjuvants in the phase Ia/Ib clinical trial.

Clinical Development

The AMA1-DiCo phase Ia/Ib clinical trial was a staggered, randomised, double-blind, multi-centre trial.

The sponsor of the clinical trial was Inserm, France. Prof Odile Launay (CIC-Cochin, Paris, France) was the principal investigator in France and Dr Sodiomon Sirima (CNRFP, Balonghin, Burkina Faso) in Burkina Faso.

The vaccination phase in France took place between January and September 2014 and the phase Ia subjects were followed until March 2015. In Burkina Faso, the vaccination phase was from July 2014 to February 2015 and the phase Ib subjects were followed until July 2015.

The clinical trial was registered on ClinicalTrials.gov NCT02014727 and www.pactr.org PACTR201402000719423.

Capacity strengthening, Workshops, Training

EVI supported Inserm, the clinical trial sponsor, in providing the fast-track clinical trial design, in reviewing all clinical trial documentation, in supervising the vaccine accountability and overviewing of the clinical trial progress until its completion.

Harmonisation

Inserm, CIC Cochin, CNRFP and BPRC AMA1-DiCo team partners have continued harmonisation of the immunological assays of the AMA1-DiCo phase Ia/Ib clinical trial.

Outreach and Communication

Sirima SB, Durier C, Kara L, Houard S, Gansane A, Loulergue P, Bahuaud M, Benhamouda N, Nebié I, Faber B, Remarque E, Launay O; AMA1-DiCo Study Group. Safety and immunogenicity of a recombinant *Plasmodium falciparum* AMA1-DiCo malaria vaccine adjuvanted with GLA-SE or Alhydrogel® in European and African adults: A phase 1a/1b, randomized, double-blind multi-centre trial. Vaccine. 2017 Oct 27;35(45):6218-6227

P27A

P27A is an unstructured 104mer synthetic peptide from *P. falciparum* PFF0165c blood-stage protein found to be the target of human antibodies inhibiting parasite growth in an antibody-dependent mechanism.

P27A was selected as by Giampietro Corradin at UNIL malaria blood stage vaccine candidate through genome mining search. The P27A peptide was synthetized and found to be highly antigenic and the target, at high prevalence, of B and T cell responses in individuals living in malaria-endemic areas. The antibodies developed by protected individuals were predominantly cytophilic IgG1 and IgG3 able to inhibit parasite growth in an antibody-dependent cellular fashion (ADCI). A multivariate analysis of immune response from both protected and unprotected individuals following natural exposure showed that P27A elicited antibodies strongly associated with naturally occurring protection[15]. The total budget for the development of P27A was up to €1,707,741 from an Irish Aid grant. An EDCTP grant of €799,480 supported the phase Ib clinical trial in Tanzania and was complemented by co-funding from BMBF (Germany).

PARTNERS

- ALMAC Sciences, United Kingdom
- Centre hospitalier universitaire vaudois (CHUV), Switzerland
- CiToxLAB, France
- European Vaccine Initiative (EVI), Germany
- Gregory Fryer Associates Ltd, United Kingdom
- Ifakara Health Institute (IHI), Tanzania
- Infectious Diseases Research Institute (IDRI), United States of America
- Nova Laboratories, Ltd, United Kingdom
- Output Pharma, Germany
- Swiss Tropical and Public Health Institute (Swiss-TPH), Switzerland
- University of Lausanne (UNIL), Switzerland

P27A vaccine candidate was evaluated in a phase Ia/Ib clinical trial. The objective was to assess the safety and immunogenicity of the P27A peptide vaccine with the aim to induce a protective antibody response that may complement

15. Olugbile *et al.*, Infection and Immunity 2009, doi:10.1128/IAI.00652-09

immune responses induced by antigens(s) from the pre-erythocytic stage in a multicomponent vaccine.

The trial was a staggered, randomized, antigen and adjuvant dose-finding, two-centre phase Ia/Ib clinical trial using the fast-track strategy set by EVI and its partners to accelerate vaccine clinical development. The trial started in Switzerland and after evaluation of the safety data of the first dose in the European volunteers, the trial started in Tanzania. P27A antigen (10 or 50µg), adjuvanted with Alhydrogel® or GLA-SE (2.5 or 5µg), or control rabies vaccine (Verorab®) were administered intramuscularly to 16 malaria non-exposed and 40 exposed subjects on days 0, 28 and 56.

The P27A vaccine was well tolerated and induced a robust specific antibody response able to recognize PFF0165c in infected erythrocytes and to inhibit parasite growth through an ADCI dependent mechanism. This was more pronounced when 50µg of P27A was formulated with GLA-SE 5µg. Incidence of adverse events and antibody responses were significantly lower in malaria-exposed Tanzanian than in non-exposed European subjects.

RECENT ACHIEVEMENTS The publication of the P27 phase Ia/Ib trial is in preparation.

P27A

Delivery Platform, Adjuvants and Viral Vectors

Glucopyranosyl Lipid A Adjuvant (GLA)-Stable Emulsion (SE) (IDRI) and aluminium hydroxide (Alhydrogel®) as a comparator are have being used as adjuvants in the phase Ia/Ib clinical trial.

Clinical Development

The P27A phase Ia/Ib clinical trial is a staggered, randomised, single-blind, antigen and adjuvant dose-finding, multi-centre trial.

The sponsor of the clinical trial was CHUV, Switzerland. Prof François Spertini (CHUV, Switzerland) was the principal investigator in Switzerland and Dr Seif Shekalaghe (IHI, Bagamoyo, Tanzania) in Tanzania.

The vaccination phase in Switzerland took place from March to July 2014 and the phase Ia subjects were followed until January 2015. In Tanzania, the vaccination phase took place from July to December 2014 and the phase Ib subjects were followed until July 2015.

This trial was registered in clinicaltrials.gov (NCT01949909) and www.pactr.org (PACTR201310000683408).

Capacity strengthening, Workshops, Training

EVI supported the clinical trial sponsor CHUV in developing the fast-track clinical trial design, in reviewing all clinical trial documentation, in supervising the vaccine accountability and overviewing of the clinical trial management until its completion.

Catherine Mkindi registered as PhD student at the University of Basel and continued her research focusing on the analysis of immune responses induced by the malaria peptide P27A delivered with either Alhydrogel or GLA-SE in Tanzanian subjects. The PhD fellowship was partly supported by an EDCTP grant for the phase Ib arm of the phase I clinical trial.

Harmonisation

P27A CHUV and IHI P27A team partners have continued the harmonisation of immunological assays used during the P27A phase Ia/Ib clinical trial.

SEmalvac

The *P. falciparum* serine repeat antigen-5 (SERA5) is an abundant blood-stage antigen that plays an essential role in the parasite life cycle and was among the first physiological substrates identified for a serine protease involved in parasite egress.

A recombinant form of the SERA5 N terminal domain (SE36) was selected for clinical development as blood stage malaria vaccine on the basis of the following results:

- Epidemiological studies showing high antibody titres that inversely correlate with malaria symptoms and severe disease.
- *In vitro* studies demonstrating the induction of antibodies that are inhibitors of parasite growth, exert antibody-dependent complement-mediated lysis of schizonts, or antibody-dependent monocyte-mediated parasite growth inhibition; and
- Animal studies demonstrating protection against *P. falciparum* challenge in NHP.

SE36 was produced in *E. coli* and further formulated under GMP conditions with aluminium hydroxide gel to yield the BK-SE36 vaccine. The safety and immunogenicity of the BK-SE36 vaccine was demonstrated in a phase Ia clinical trial in malaria-naïve Japanese adults and in a phase Ib clinical trial conducted in healthy subjects aged 6–32 years from a malaria-endemic area in Northern Uganda.

The main objective of the SEmalvac project supported by the GHIT Fund ($999,999) and by Nobelpharma Co., Ltd ($500,000) is to assess the safety and immunogenicity of the BK-SE36 vaccine candidate in healthy malaria exposed African children aged 1-5 years living in Burkina Faso. This phase Ib trial will allow to test the vaccine in a younger age group (1-5 years), generate additional data on safety, immunogenicity and allow comparison of clinical trial results from two countries with different malaria endemicity - Uganda (previous clinical trial) and Burkina Faso. The trial is a double blinded, randomized, controlled, age deescalating, phase Ib trial using either intramuscular or subcutaneous vaccination of BK-SE36 vaccine (100µg SE36 and 1000µg aluminium). The participants aged 12-24 months or 25-60 months received the vaccine on three occasions and were followed for one year.

PARTNERS

- Centre national de recherche et de formation sur le paludisme (CNRFP), Burkina Faso
- European Vaccine Initiative (EVI), Germany
- Research Institute for Microbial Diseases (RIMD), Japan
- Nobelpharma Co, Ltd, Japan
- Pharmalys, United Kingdom/Senegal
- London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom

A second objective of the SEmalvac project is to conduct a one year follow-up study of Japanese volunteers that participated in the first-in-man phase I a trial of BK-SE36 vaccine combined with CpG-ODN (K3) adjuvant that is expected to enhance immune response, to assess the vaccine long term safety and immunogenicity.

The phase Ib clinical trial began in July 2015 with the immunisation of children aged 2–5 years old. The last

Delivery Platform, Adjuvants and Viral Vectors

The malaria antigen SE36 is adsorbed onto aluminium hydroxide gel in the BK-SE36 vaccine manufactured at BIKEN (Japan).

Clinical Development

The age de-escalating phase Ib clinical trial was designed to assess the safety and immunogenicity of the recombinant *E. coli* BK-SE36 malaria vaccine candidate in healthy malaria-exposed African children aged 1–5 years living in Burkina Faso. The principal investigator is Dr Sodiomon Sirima (CNRFP, Ouagadougou, Burkina Faso) and the sponsor is Nobelpharma Co Ltd. (Japan).

The vaccination of the children aged 2–5 years started in July 2015. After the second vaccination, a safety report was provided to an independent safety monitoring committee which recommended that vaccination could proceed in the younger population aged 1–2 years. The vaccination of the younger cohort started in October 2015 and was completed in April 2016. The follow-up period was completed in February 2017.

The clinical trial is registered www.pactr.org (PACTR201411000934120).

boost immunisation of the younger population aged 1–2 years was administered in April 2016 and the trial follow-up phase was completed in February 2017.

RECENT ACHIEVEMENTS Safety data and IgG titres collected until one month after the last immunisation indicate that BK-SE36 vaccine is safe, well tolerated and immunogenic. The vaccine induced an immune response with IgG titres that increased following the second immunisation and after the booster dose, indicating the need of a booster dose in malaria endemic areas. As anticipated, the increase in SE36 specific IgG titres after the vaccinations was more pronounced in the younger cohort (12-24 months) than in older children (25-60 months) and this was observed for both intramuscular and subcutaneous route of vaccination.

After one year follow-up of malaria naïve Japanese adults vaccinated with the BK-SE36/CpG vaccine, no change was observed in the laboratory indicators of autoimmune disease confirming the safety of the vaccine. Moreover, IgG titres elicited by the vaccine remained high after one year.

SEmalvac2

The SEmalvac2 project builds on the SEmalvac project and is the continuation of the clinical development of the BK-SE36 vaccine. It is intended to explore if the immunogenicity of the vaccine can be further improved with the addition a DNA sequences containing CpG motifs.

K3 CpG in non-human primate studies was identified as an effective TLR9 ligand that can induce both humoral and cellular immunity when compared to BK-SE36 alone[16]. The use of K3 CpG may be one approach to broaden immune responses and may overcome immune tolerance or help immunocompromised individuals through the activation of multiple innate receptors that could target redundant pathways of innate responsiveness[17]. The BK-SE36 vaccine mixed with K3 CpG (BK-SE36/CpG) vaccine was assessed in a phase Ia clinical trial in healthy adults in Japan and was found safe and elicited antibody titres 3-4-fold higher than BK-SE36 alone. Sera of vaccinated volunteers inhibited *in vitro* parasite growth.

The SEmalvac2 project, supported by GHIT ($2,781,588) and by Nobelpharma Co, Ltd, aims at assessing the safety and immunogenicity of the BK-SE36/CpG vaccine in healthy malaria exposed African adults and children living in Burkina Faso. This phase Ib clinical trial is an age de-escalation trial where the BKG/SE36/CpG vaccine safety will be first evaluated in adults aged 21-45 years before proceeding to younger populations of children aged 5-10 years and 12-24 months.

RECENT ACHIEVEMENTS The BK-SE36/CpG phase Ib trial received favourable opinion from the national ethics committee of Burkina Faso and by ethics committee of LSHTM and RIMD in November 2017.

PARTNERS

- Institut de Recherche en Sciences de la Santé (IRSS), Burkina Faso
- European Vaccine Initiative (EVI), Germany
- Research Institute for Microbial Diseases (RIMD), Japan
- Nobelpharma Co, Ltd, Japan
- Pharmalys, United Kingdom/Senegal
- London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom

SEmalvac2

Delivery Platform, Adjuvants and Viral Vectors

The malaria antigen SE36 is adsorbed onto aluminium hydroxide gel in the BK-SE36 vaccine manufactured at BIKEN (Japan) and mixed prior to administration with K3 CpG manufactured at Gene Design (Japan).

Clinical Development

The age de-escalating phase Ib clinical trial is designed to assess the safety and immunogenicity of the BK-SE36/CpG vaccine in healthy malaria exposed African adults and children living in Burkina Faso. The principal investigator is Dr Sodiomon Sirima (IRSS, Ouagadougou, Burkina Faso) and the sponsor is Nobelpharma Co Ltd. (Japan).

The clinical trial is registered www.pactr.org (PACTR201701001921166)

16. Tougan T *et al.* 2013. Hum Vaccin Immunother. 9(2):283-290.
17. Scheiermann J, Klinman DM. Vaccine. 2014 Nov 12;32(48):6377-89. doi: 10.1016/j.vaccine.2014.06.065

MALARIA BLOOD-STAGE VACCINES THAT PREVENT

placental malaria

Placental malaria is a major health problem manifesting as severe disease and anaemia in the mother, impaired foetal development, low birth weight or spontaneous abortion. While women living in malaria endemic areas gradually develop immunity to clinical malaria, women become susceptible to placental malaria during their first pregnancy. Every year, more than 100 million pregnant women are at risk of placental malaria, which causes the deaths of approximately 80,000–200,000 children[18].

Prevention of placental malaria currently relies on intermittent preventive treatment during pregnancy (IPTp) and long lasting insecticide treated nets. However, these interventions only offer partial protection. Indeed, sulfadoxine-pyrimethamine used for IPTp is losing its effectiveness due to parasite resistance and women receive their first IPTp dose at their first antenatal visit (between 16-24 weeks' gestation)[19],[20],[21]. As placental parasite tropism is established during the first trimester of pregnancy, parasites cause irreversible damage, probably by impeding placental development, before women access antenatal healthcare. Therefore, an effective vaccine that prevents *P. falciparum* placental malaria would be an attractive, cost-effective complement to prevent placental malaria.

Placental malaria is caused by parasite-infected red blood cells adhering to the placental receptor Chondroitin Sulfate A (CSA), and their subsequent accumulation in the placenta, from where they can cause disease and death for the mother and her offspring. Fortunately, women can acquire immunity against placental malaria and in malaria-endemic areas the average birth weight is significantly higher among second and third babies compared to the first born[22],[23]. This relatively fast acquisition of protection has raised hope that a vaccine for placental malaria can be developed.

EVI has raised funds from BMBF, Institut national de la santé et de la recherche médicale (Inserm), the EU and the Danish National Advanced Technology Foundation (HTF) through University of Copenhagen (UCPH), with further co-funding from Irish Aid, Department of Foreign Affairs and Trade (Ireland) and has set up and reinforced collaboration with NIH-NIAID. The three most advanced groups dealing with this target are therefore collaborating on the development of a placental malaria vaccine. The two vaccine candidates under development offer hope that the burden of malaria in pregnant women can be reduced, improving the health of mothers and newborns.

18. Hartman *et al.*, Annals of Tropical Paediatrics 2010, doi:10.1179/146532810X12858955921032
19. Doritchamou *et al.*, J Infect Dis. 2012 Dec 15;206(12):1911-9.
20. Schmiegelow *et al.*, PLoS ONE. 2013;8(1):e53794.
21. Moussiliou *et al.*, Malar J. 2013;12:195.
22. Brabin *et al.*, Bull World Health 1983 PMC2536236
23. McGregor *et al.* Transactions of the Royal Society of Tropical Medicine and Hygiene 1983 doi: 10.1016/0035-9203(83)90081-0

The target product profile for placental malaria vaccines differs from standard malaria vaccines. Placental malaria 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 human papilloma virus. Depending on the other malaria vaccines available on the market, a placental malaria vaccine could also be associated with a booster dose of a 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 the variant surface antigen that mediates adhesion of the infected erythrocyte to CSA (VAR2CSA) as a leading candidate for the placental malaria vaccine[24],[25]. This is a *P. falciparum* Erythrocyte Membrane Protein-1 (PfEMP1) adhesin encoded by member of the *var* gene family, and is specifically expressed by placental parasites. Women acquire antibodies against VAR2CSA over successive pregnancies as they become resistant to placental malaria[26]. 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 Duffy-Binding-Like (DBL) domains and a cysteine-rich inter-domain, interspersed with short inter-domain regions. DBL3X is the principal target of inhibitory antibodies that prevent parasite adhesion to CSA[27],[28]. 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[29],[30]. These data indicate that vaccines designed to block interactions between the parasite and CSA should be based on the N-terminal region of VAR2CSA.

24. Baruch *et al.*, Cell 1995 doi:10.1016/0092-8674(95)90054-3
25. Su *et al.*, Cell 1995 doi:10.1016/0092-8674(95)90055-1
26. Fried *et al.*, Nature 1998, doi:10.1038/27570
27. Avril *et al.*, Malaria Journal 2011; doi:10.1186/1475-2875-10-36
28. Dahlback *et al.*, J Biol Chem 201, doi:10.1074/jbc.M110.1915101
29. Bordbar *et al.*, Bioelectrochemistry 2011, doi:10.1016/j.bioelechem.2011
30. Bigey *et al.*, J Inf Dis 2011, doi:10.1093/infdis/jir499

PlacMalVac

The conduct of a phase I clinical trial with the PAMVAC vaccine was one objective of the EU funded PlacMalVac project with budget of approximately €5,900,000. Another objective was the preparation of a phase II trial. The project started in March 2013 and ended in February 2017.

RECENT ACHIEVEMENTS The main achievement of 2017 was the trial termination in August 2017 after the vaccination and follow up of the malaria naive subjects in Germany and the malaria exposed subjects in Benin.

PARTNERS

- University of Tübingen (EKUT), Germany
- European Vaccine Initiative (EVI), Germany
- ExpreS2ion Biotechnologies, Denmark
- University of Copenhagen (UCPH), Denmark
- Institut de recherche pour le développement (IRD), France
- Université d'Abomey-Calavi (UAC), Benin

Delivery Platform, Adjuvants and Viral Vectors

The adjuvants used in the clinical trial are aluminium hydroxide (Alhydrogel®), the GLA-SE and GLA-Liposome-QS21 formulation (LSQ). Alhydrogel® was filled by EVI at Nova Laboratories Ltd and GLA-SE and GLA-LSQ were manufactured at IDRI, Seattle, USA.

Clinical Development

The phase Ia/Ib clinical trial was staggered randomised, controlled and dose-finding trial. It was designed to assess the safety and immunogenicity of different dosages (20, 50 and 100µg) of the PAMVAC VAR2CSA vaccine in healthy adult subjects not exposed to malaria in Germany and in exposed subjects living in malaria-endemic areas in Benin. The PAMVAC vaccine was mixed prior to administration with aluminium hydroxide or GLA-SE or GLA-LSQ.

The sponsor was EKUT (Tübingen, Germany), the principal investigator in Germany was Dr Benjamin Mordmüller (EKUT). Principal investigator in Benin was Dr Saadou Issifou (Institut de recherche clinique du Bénin, Cotonou).

The trial began in Germany in July 2015, proceeded in Benin in March 2016 and ended in August 2017. Each dosage escalation was conditioned by safety assessment performed by an independent safety monitoring board. Preliminary analyses indicated that the vaccine was well tolerated and immunogenic, complete data analyses including the functionality of the induced antibodies is underway.

The trial is registered in clinicaltrials.gov (NCT02647489).

Capacity strengthening, Workshops, Training

EVI supported the sponsor EKUT in providing the fast-track clinical trial design, continued assistance in the setting of the quality assurance system of the sponsor as well as the phase Ia clinical trial site and the implementation of the quality assurance system in the phase Ib new clinical trial site in Benin.

Harmonisation

EVI contributed to efforts toward clinical trial immunoassay harmonisation.

Outreach and Communication

Gbédandé K, Fievet N, Viwami F, Ezinmegnon S, Issifou S, Chippaux JP, Dossou Y, Moutairou K, Massougbodji A, Ndam N, de Jongh WA, Søgaard TMM, Salanti A, Nielsen MA, Esen M, Mordmüller B, Deloron P, Luty AJF; Multi-centre research paper. Clinical development of a VAR2CSA-based placental malaria vaccine PAMVAC: Quantifying vaccine antigen-specific memory B & T cell activity in Beninese primigravidae. Vaccine. 2017 Jun 14;35(27):3474-3481. doi: 10.1016/j.vaccine.2017.05.027

Pehrson C, Salanti A, Theander TG, Nielsen MA. Pre-clinical and clinical development of the first placental malaria vaccine. Expert Rev Vaccines. 2017 Jun;16(6):613-624. doi: 10.1080/14760584.2017.1322512.

Pehrson C, Heno KK, Adams Y, Resende M, Mathiesen L, Soegaard M, de Jongh WA, Theander TG, Salanti A, Nielsen MA. Comparison of functional assays used in the clinical development of a placental malaria vaccine. Vaccine. 2017 Jan 23;35(4):610-618. doi: 10.1016/j.vaccine.2016.12.028.

MORTEN A. NIELSEN

Morten A. Nielsen M.Sc., PhD is associate professor at the Centre for Medical Parasitology (CMP), University of Copenhagen.

CMP, one of the leading malaria vaccine research institutions, has received an excellence award from the University of Copenhagen to study PfEMP1 structure and function. This has allowed the identification of lead malaria candidates such as VAR2CSA and PfEMP1 types causing severe malaria that have been described in numerous peer reviewed international journals. CMP is a key player in a number of EU research projects aimed at describing the malaria disease syndrome and testing potential vaccine in clinical trials. This work has to a high degree been facilitated by EVI. CMP is in line with the vision of EVI being highly involved in capacity building in Africa and working closely together with universities located in Tanzania, Ghana and Benin. CMP participated in the RTS,S vaccine phase III clinical trial in Tanzania and is currently finalising a phase I clinical trial of the PAMVAC VAR2CSA vaccine in Germany and Benin (PlacMalVac project). CMP has also recently finalized the first phase II clinical trial with a malaria blood stage vaccine targeting GLURP and MSP2.

Morten's personal area of research has focused on the acquisition of the immunity against malaria. The study of antigens inserted into the red blood cell membrane by the infecting *Plasmodium falciparum* parasite and how they mediate adhesion to host receptors has been pivotal for this research. Morten has been leading the work taking the VAR2CSA antigen from discovery to clinical trials. Importantly, this resulted in the identification of the regions of this large antigen that mediate binding to the placental receptor CSA that has opened the path of the development of a potential vaccine against placental malaria. In addition, this has led to the important discovery that this form of CSA is also present on the surface of most cancer types suggesting that it will be possible to diagnose and treat cancer using VAR2CSA antigen. Furthermore, acknowledging difficulties in inducing potent and long-lasting immune responses against recombinant soluble proteins, the team has over the last decade invested significantly in developing novel methods to deliver vaccines. This has resulted in a proprietary virus-like particle (VLP) vaccine- platform that holds the promise to deliver virtually any complex polypeptide in the most optimal way on the surface of the VLP. The team is currently with the aid of EVI seeking funding to further develop our placental vaccine using this novel VLP platform.

PRIMALVAC

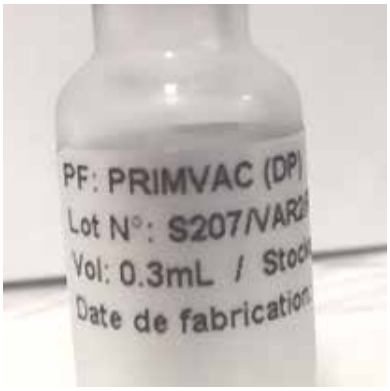
PRIMALVAC aims to develop a placental malaria vaccine to improve pregnancy outcomes. The main objective is to obtain proof of concept that VAR2CSA-based vaccines induce long-lasting or rapidly-boosted cross-reactive and inhibitory antibodies. Recombinant forms of VAR2CSA were generated, and their immunogenic activity was assessed specifically for their ability to elicit functional and cross-reactive antibodies against placental forms of the parasite. The candidate antigen that best meet strict immunogenicity criteria was moved into preclinical and clinical development.

PRIMALVAC has a total budget of €7,180,606.93 provided by the BMBF through Kreditanstalt für Wiederaufbau (KfW), EVI, Inserm, the Institut national de la transfusion sanguine (INTS) and Irish Aid, Department of Foreign Affairs and Trade (Ireland). The project started in December 2011, activities are on-going.

RECENT ACHIEVEMENTS A total of 68 subjects were recruited in four cohorts receiving three vaccinations with 20, 50 or 100 µg of PRIMVAC adjuvanted with Alhydrogel or GLA-SE or placebo at one month intervals. The one year follow-up period in the phase Ia arm of the clinical trial in France was completed in September 2017. In Burkina Faso, follow-up is on-going.

PARTNERS

- 4Clinics, France
- BIOTEM, France
- Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso
- Centre d'investigation clinique en Vaccinologie Cochin-Pasteur (CIC1417), France
- CiToxLAB, France
- Creapharm, France
- EUropean CLInical Trials Platform & Development, France
- European Vaccine Initiative (EVI), Germany
- French Clinical Research Infrastructure Network (F-CRIN), France
- GTP Technology, France
- Infectious Diseases Research Institute (IDRI), United States of America
- Institut national de la santé et de la recherche médicale (Inserm), France
- Nova Laboratories, United Kingdom
- Novasep (formerly Henogen), Belgium
- Novavax, United States of America (formerly ISCONOVA, Sweden)
- Output Pharma, Germany
- Pfenex Inc., United States of America
- Voisin Consulting Life Sciences, France



Preclinical, process development, production, IMPD

Recombinant proteins encompassing the VAR2CSA high affinity CSA-binding site were previously generated. Analysis of the functionality and cross-reactivity of the induced antibodies allowed down-selection of the 3D7-DBL1X-2X expressed in *E. coli* as the best antigen to be transitioned to clinical development. Novasep manufactured the GMP batch of PRIMVAC and the PRIMVAC drug product was released. Short-term and accelerated stability studies were performed and long-term stability studies are ongoing at Novasep, allowing a shelf-life extension to March 2018. Toxicology studies were conducted by CiToxLAB and the final report is available. The IMPD and IB have been completed.

Delivery Platform, Adjuvants and Viral Vectors

The selected adjuvants are aluminium hydroxide (Alhydrogel®) and GLA-SE. A clinical supply agreement was signed by Inserm and IDRI. The GLA-SE was released in Europe by Output Pharma for clinical trial use. Alhydrogel® filled by EVI at Nova Laboratories Ltd. is used for the clinical trial.

Clinical Development

The PRIMALVAC project is currently carrying out a phase Ia/Ib clinical trial in healthy adult subjects naïve to malaria and in exposed subjects in malaria-endemic regions of sub-Saharan Africa. The inventor of the vaccine is Dr Benoît Gamain and the sponsor of the clinical trial is Inserm. The coordinating investigator is Prof Odile Launay (CIC1417, Paris, France), the principal investigators of the clinical trial are Dr Pierre Loulergue (CIC1417, Paris, France) and Dr Sodiomon Sirima (CNRFP, Balonghin, Burkina Faso). The clinical trial is designed to assess the safety and immunogenicity of different doses of the recombinant VAR2CSA DBL1-2 vaccine candidate (PRIMVAC) in Alhydrogel® or GLA-SE. The primary objective of the study is to evaluate the safety of 3 different dosages (20µg, 50µg and 100µg) of the PRIMVAC vaccine adjuvanted either with Alhydrogel® or GLA-SE, and administered at D0, D28 and D56. Immunogenicity of the vaccine is explored as secondary objective. Within four sequential cohorts, volunteers were randomized in two arms (PRIMVAC adjuvanted with Alhydrogel® or GLA-SE) in the first phase conducted in France and then in three arms (PRIMVAC with Alhydrogel® or GLA-SE or placebo) in Burkina Faso.

Authorisation for the clinical trial in France was obtained by the end of 2015; the site initiation visit was performed in January 2016. The first vaccination of the first subject in France was on 9 May 2016, follow-up was completed in September 2017. No Serious Adverse Event (SAE) was reported in any of the cohort A volunteers and enrolment in cohort B started. A DSMB meeting took place in September 2016 to review the safety data obtained for cohort A (20µg) and B (50µg) and the DSMB recommended the continuation of the protocol in its current version with progression to the cohort C (50µg) in Burkina Faso. The phase Ib clinical trial at CNRFP in Burkina Faso received full authorisation in September 2016 and the phase Ib clinical trial arm started in November 2016. Another DSMB meeting in June 2017 recommended the progression from cohort C to cohort D (100µg). Last vaccination of the last subject in cohort D occurred in September 2017. Preliminary safety and immunogenicity results of the first placental malaria vaccine phase Ia/b clinical trial in France and Burkina Faso will be available in Q2 2018.

The trial is registered in clinicaltrials.gov: NCT02658253.

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PRIMALVAC

Harmonisation

EVI contributed to the efforts towards clinical trial immunoassay harmonisation of placental malaria vaccines. A workshop report summarising the outcomes was published in Malaria Journal: Chêne A, Houard S, Nielsen MA, Hundt S, D'Alessio F, Sirima SB, Luty AJ, Duffy P, Leroy O, Gamain B, Viebig NK. Clinical development of placental malaria vaccines and immunoassays harmonization: a workshop report. Malar J. 2016 Sep 17;15:476.

Capacity strengthening, Workshops, Training

EVI supported and mentored the clinical trial sponsor, Inserm, during the set-up and conduct of the pharmacotoxicological studies, during the preparation of the dossiers relevant for the clinical trial (e.g. IB, IMPD, clinical trial protocol), and during the manufacture, the release of the drug product and adjuvants to the clinical trial and/or clinical trial activities.

Outreach and Communication

Benoît Gamain presented "Développement d'un vaccin contre le paludisme Gestationnel" at the 11ème Journée I-REIVAC "Vaccination et maladies infectieuses émergentes", 24 March 2017, Paris, France.

BENOÎT GAMAIN

Dr Benoît Gamain holds a PhD in Parasitology and is a CNRS senior scientist and Principal Investigator of the Severe Malaria Pathogenesis Group in the Inserm Unit UMR_S 1134 localised at the National Institute of Blood Transfusion, Paris. He started his career as a post-doctoral fellow working on malaria in Dr Louis Miller's laboratory at the National Institutes of Health, Bethesda 1998 – 2003. Benoît then received a permanent position at Centre National de la Recherche Scientifique (CNRS) and joined Prof Artur Scherf's laboratory (Institut Pasteur). Since 2010, Benoît joined the Inserm Unit UMR_S 1134 where he heads the Severe Malaria Pathogenesis team.

His laboratory works on the identification of the host-parasite interactions involved in the parasite adhesive processes leading to severe clinical forms of malaria such as placental malaria. The main objective of the Severe Malaria Pathogenesis team is to develop a functional vaccine to protect pregnant women from the devastating consequences of placental malaria. His research efforts focus on the identification and the deciphering of the molecular interactions involved in the parasite adhesion processes, to provide a rational basis for accelerating vaccine and therapeutic developments to inhibit *Plasmodium falciparum* infected erythrocytes sequestration. Understanding further the functional characteristics of VAR2CSA expressed by placental parasites at the molecular level will provide a rational basis for accelerating vaccine and therapeutic developments to inhibit infected erythrocytes sequestration in the placenta.

In close collaboration with EVI, he down-selected and moved the PRIMVAC vaccine candidate from the preclinical development to phase I clinical trial in France and Burkina Faso. Dr Gamain says "Our collaboration with EVI has started 15 years ago! Without their great expertise in vaccine development and their commitment to fight malaria we would never have the PRIMVAC vaccine in a phase I clinical trial today. I'm highly optimistic that our collaboration will continue in the next years to move PRIMVAC in a phase II multicentric clinical trial".

PlacID

The overall objective of PlacID is to validate a novel non-human primate model to evaluate the placental malaria vaccine candidates and to assess this model as a platform for testing placental malaria vaccine candidates prior to human testing. The lack of a reliable preclinical model for placental malaria in the past has significantly delayed the development of placental malaria vaccines.

The LMIV, NIH/NIAID has established a non-human primate model of placental malaria that for the first time reproduces all the features of *P. falciparum* malaria in pregnant women. Members of the genus *Aotus* are among the few species that are affected by *P. falciparum*, making them suitable for non-human primate experimental models in malaria research. Importantly, the animals in this model develop broadly neutralising antibodies over successive episodes of placental malaria, as do women, suggesting that this may be an appropriate model for preclinical qualification and the down-selection of vaccine candidates.

PARTNERS

- European Vaccine Initiative (EVI), Germany
- Institut national de la santé et de la recherche médicale (Inserm), France
- National Institute of Allergy and Infectious Diseases (NIAID) - Laboratory of Malaria Immunology and Vaccinology (LMIV), United States of America
- University of Copenhagen (UCPH), Denmark

The specific objectives of PlacID are:

- To confirm that the passive transfer of purified immune IgG from multigravid African women will confer protection in pregnant *Aotus* monkeys when they are exposed to placental infection with *P. falciparum*.
- To conduct a vaccination study that assesses the leading placental malaria vaccine candidates, including the two candidates from the EVI portfolio, as well as appropriate controls.

The project started in July 2015 with a total project budget of €866,720.99. Activities are on-going.

RECENT ACHIEVEMENTS Passive transfer commenced in 2015 and the team is expecting to unblind the study and obtain the first set of data in Q2 2018. In the vaccination studies, all animals were vaccinated and follow-up will continue in 2018. First unblinded results are expected in Q2 2018.

Delivery Platform, Adjuvants and Viral Vectors

The placental malaria vaccine candidates PAMVAC, PRIMVAC and the pre-clinical NIH/NIAID vaccine candidate as well as a control antigen were adjuvanted with aluminium hydroxide (Alhydrogel®).

Preclinical Development

Passive immunity studies using IgG from malaria-immune multigravid women and malaria-naïve individuals were initiated in the *Aotus* non-human primate model in November 2015. An interim analysis is planned by the biostatistician in Q2 2018 when three monkeys in each of the two groups have reached the endpoint "placental parasitaemia" after caesarean section.

In the vaccination study, all the vaccinations with PAMVAC, PRIMVAC and the NIH/NIAID vaccine candidate were completed and the follow-up is ongoing. The primary endpoint of this study is induction and boosting of functional antibodies. Secondary endpoint is placental parasitaemia. Most of the immunological analyses were performed at NIH/NIAID, but the study will remain blinded until the biostatistician has performed an interim analysis and proposed a study end. All vaccinations are completed, 22 monkeys have completed pregnancy with nine premature deliveries and thirteen caesarean sections allowing to assess the primary endpoint of this study: induction and boosting of functional antibodies. Interim results are expected in Q2 2018.

Capacity strengthening, Workshops, Training

During the PlacID project, good animal handling practices were established as evidenced by the high pregnancy rate of the *Aotus* animals at NIAID-LMIV. This is a particular achievement appreciated by the scientific community. Despite that the animals are handled on a regular basis for ultrasound examinations and sampling, the pregnancy rate has been even higher than that expected in a breeding colony.

Harmonisation

The PlacID project is a close collaboration of the major teams leading the efforts in developing a placental malaria vaccine. The PAMVAC, PRIMVAC and a preclinical NIH/NIAID vaccine candidate are evaluated side-by-side in the vaccination studies. Reagents and parasite lines were exchanged by the teams and protocols for various assays and data analysis were shared and aligned.

MALARIA VACCINES THAT PREVENT INFECTION AND MORBIDITY/MORTALITY: Combination vaccines

The Malaria Vaccine Technology Roadmap that was updated in 2013[31] defined the strategic goals for 2030 as licensed vaccines targeting *P. falciparum* and *P. vivax* with the following objectives:

- To develop malaria vaccines with protective efficacy of at least 75 percent against clinical malaria suitable for administration to appropriate at-risk groups in malaria-endemic areas.
- To develop malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection.

The development of a highly effective subunit malaria vaccine suitable for widespread deployment is likely to require a multi-component vaccine including antigens from more than one stage of the parasite's life cycle as indicated in the "WHO Preferred Product Characteristics (PPC) for Malaria Vaccines"[32]. This strategy could overcome the limited efficacy of single antigen components. Critical aspects to consider are the choice of the most suitable combination of vaccine components, delivery systems and adjuvants suitable for all components, and the design of combination vaccine clinical trials. Vaccine candidates that have already demonstrated efficacy are currently the most suitable candidates for multi-component and multi-stage vaccines[33].

MultiMalVax

MultiMalVax is a pan-European project that is addressing shortcomings in the fight against malaria. MultiMalVax partners comprised five European organisations involved in vaccine development, each contributing with specialised expertise and technology.

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

The EU FP7 funded MultiMalVax project started in October 2012 with a budget of €8,000,000. This collaboration included one Small and Medium Enterprise (SME), two universities, one global pharmaceutical company and EVI, and provided complementary abilities to facilitate the development of this promising vaccine product.

RECENT ACHIEVEMENTS MultiMalVax successfully completed first-in-human phase I clinical trials for the adjuvanted sporozoite-stage malaria vaccine candidate R21, the blood-stage antigen PfRH5 and the transmission blocking vaccine candidate Pfs25, to complement the already available ME-TRAP vectored liver-stage vaccine candidates. This was completed by combination phase I/II clinical trials assessing GSK's RTS,S administered with vectored ME-TRAP as well as R21 in adjuvant administered with or without vectored ME-TRAP. All approaches have shown favourable safety and immunogenicity profiles and important positive efficacy data was achieved in 2017 with a new vaccine candidate. Progress was also made in the establishment of a functional *in vitro* assay that allows quantification and further analyses of the immunological responses induced by liver-stage vaccines.

PARTNERS

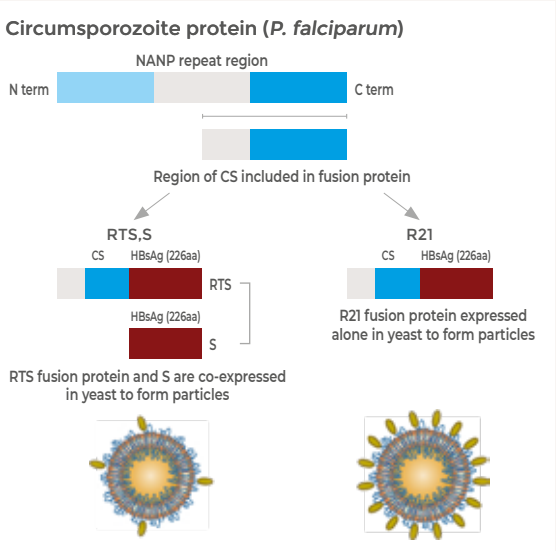
- European Vaccine Initiative (EVI), Germany
- GlaxoSmithKline (GSK) (formerly Novartis Vaccines and Diagnostics s.r.l., Italy, acquired by GSK), Belgium
- ReiThera s.r.l. (formerly Okairòs s.r.l.,), Italy
- Université Pierre et Marie Curie (UPMC), France
- University of Oxford (UOXF), United Kingdom

31. http://www.who.int/immunization/topics/malaria/vaccine_roadmap/TRM_update_nov13.pdf?ua=1
32. http://apps.who.int/iris/bitstream/10665/149822/1/WHO_IVB_14.09_eng.pdf
33. Viebig N.K. *et al.* Vaccine 2015, doi:10.1016/j.vaccine.2015.09.074.

Delivery Platform, Adjuvants and Viral Vectors

The malaria antigens ME-TRAP, PfRH5 and Pfs25 were designed to be delivered in a prime boost strategy using two different vectors: ChAd63 and MVA. The transmission-blocking Pfs25 antigen was fused to the Imaxio IMX313 carrier protein. Fusion to the IMX313 DNA sequence led to oligomerisation of the recombinant protein because the IMX313 carrier protein spontaneously auto-assemble into a heptamer. The oligomerisation of the antigen was expected to significantly increase both B cell and T cell immunogenicity, therefore improving vaccine efficacy. R21 was administered with the $AS01_B$ adjuvant. RTS,S adjuvanted with $AS01_B$ was provided by GSK.

FIGURE 1 GRAPHICAL ILLUSTRATION OF R21 AND RTS,S



Clinical Development

The initial ambitious objective of developing a vaccine candidate targeting each stage of the parasite life cycle was modified to a multi-component vaccine, for which a combination vaccine trial.

Safety and immunogenicity of a protein particle malaria vaccine candidate, R21, administered with $AS01_B$ in healthy UK volunteers (VAC056):
The Medicine and Healthcare products Regulatory Agency (MHRA) approved the phase I clinical trial in October 2015 and the clinical trial commenced in December 2015. R21 adjuvanted with $AS01_B$ was administered to 20 healthy volunteers in Oxford and Southampton in this phase I trial VAC056 (ClinicalTrials.gov Identifier: NCT02600975). All vaccinations were administered intramuscularly in a three-dose regime with vaccinations given 4 weeks apart. Participants were followed up for 6 months after their final vaccination. VAC056 is now completed and the last participant visit took place in January 2017. There were no safety concerns relating to R21 in GSK's $AS01_B$ adjuvant and both doses were well tolerated. R21 in $AS01_B$ was immunogenic and induced good antibody responses to the pre-erythrocytic circumsporozoite protein at both 10 and 50µg doses tested, which was comparable to levels induced by the leading malaria vaccine candidate, RTS,S. Initial immunogenicity profiles observed are very encouraging and it induces strong antibody responses to the CSP central repeat, at levels comparable to those induced by the leading malaria vaccine candidate, RTS,S. The results of this clinical trial will be published in a scientific journal in 2018.

TABLE 1 VAC056 TRIAL DESIGN

Week	0	4	8
Group 1 (n=10)	10µg R21/ $AS01_B$	10µg R21/ $AS01_B$	10µg R21/ $AS01_B$
Group 2 (n=10)	50µg R21/ $AS01_B$	50µg R21/ $AS01_B$	50µg R21/ $AS01_B$

A Phase Ia clinical trial to assess the safety and immunogenicity of new *Plasmodium falciparum* malaria vaccine candidates ChAd63 RH5 alone and with MVA RH5 (VAC057):
This phase Ia trial (ClinicalTrials.gov Identifier: NCT02181088) is a dose escalation, first-in-human trial of the viral vectored *P. falciparum* blood-stage malaria vaccine candidates ChAd63 RH5 and MVA RH5 in a heterologous prime-boost regimen. The vectored PfRH5 blood-stage vaccine clinical trial started in August 2014 and ended in October 2015. In this trial the safety and cellular and humoral immunogenicity of this vaccination regimen were assessed. ChAd63/MVA RH5 vaccines were shown to be safe and immunogenic in healthy volunteers. Purified IgG from trial volunteers inhibited *P. falciparum* growth, as assessed by a growth inhibition assay (GIA). This is the first antigen to induce substantial cross-strain GIA following viral vectored vaccination in a clinical trial. A manuscript was published in JCI Insight in November 2017. An effective RH5 vaccine is likely to require higher levels of antibodies than were induced by ChAd63/MVA RH5. A protein-in-adjuvant formulation (RH5.1) is currently being evaluated in a phase I/IIa clinical trial in the UK.

A Phase Ia clinical trial to assess the safety, immunogenicity and ex-vivo efficacy of new *Plasmodium falciparum* malaria vaccine candidates ChAd63 Pfs-IMX313 alone and with MVA Pfs25-IMX313 (VAC062):
The phase I clinical trial VAC062 is the first clinical use of the viral vectored transmission blocking/mosquito stage vaccines ChAd63 Pfs25-IMX313 and MVA Pfs25-IMX313. This phase I trial in healthy volunteers aged 18 – 50 began in 2015 and was conducted in Southampton and Oxford, UK (ClinicalTrials.gov Identifier: NCT02532049). The total number of volunteers planned for enrolment in the study was 24, with 16 of these receiving both vaccines. ChAd63 Pfs25-IMX313 was given as a prime vaccination with the MVA Pfs25-IMX313 boost given 8 weeks later. The first 8 volunteers received ChAd63 Pfs25-IMX313 alone as part of the dose escalation study design. There have been no safety concerns relating to the vaccines and they have been well tolerated. Immunogenicity analysis demonstrated that antigen-specific T cell s as well as antibodies were induced after vaccination.

A Phase I/IIa Sporozoite Challenge Study to Assess the Safety and Protective Efficacy of adjuvanted R21 at two different doses and the Combination Malaria Vaccine Candidate Regimen of adjuvanted R21 + ChAd63 and MVA encoding ME-TRAP (VAC065):
The safety, immunogenicity and efficacy of R21 adjuvanted with Matrix-M1 in comparison to R21/Matrix-M1 in combination with ME-TRAP vectored vaccines was assessed in this phase I/IIa challenge trial (ClinicalTrials.gov Identifier: NCT02905019). The R21 vaccine targets the sporozoite stage of infection and this is used in combination with the heterologous prime boost viral vector vaccine regimen of ChAd63-MVA ME-TRAP, which targets the liver-stage of infection. The total number of volunteers planned for enrolment in this malaria challenge trial was 36 plus 6 unvaccinated controls. VAC065 was conducted in Oxford and Southampton and efficacy was evaluated in a malaria mosquito bite challenge (CHMI) in January 2017. Three doses of 10µg R21 adjuvanted with Matrix-M1 given 4 weeks apart demonstrated high level sterile efficacy [(81.8%;n=11); p=0.0009]. Significantly reduced reactogenicity compared to reported data on the standard RTS,S/AS01 regimen was observed. These data provide strong support for this R21/MM vaccine to be evaluated further in African adults, children and infants. The results of this clinical trial will be published in a scientific journal in 2018.

Harmonisation

UOXF was a member of the MVVC and MVVC 2 consortia and was part of the OPTIMALVAC network and was thus involved in antibody and T cell assay harmonisation activities. In addition, phase I clinical trials assessing the transmission-blocking antigen Pfs25-IMX313 and the pre-erythrocytic R21 vaccine candidate are being conducted at the Centre for Clinical Vaccinology and Tropical Medicine, UOXF, and the Southampton National Institute for Health Research Wellcome Trust, and clinical activities are harmonised across these centres. Controlled human malaria challenges by mosquito-bite were conducted according to standardised protocols.

Outreach and Communication

Payne RO, Silk SE, Elias SC, Miura K, Diouf A, Galaway F, de Graaf H, Brendish NJ, Poulton ID, Griffiths OJ, Edwards NJ, Jin J, Labbé GM, Alanine DG, Siani L, Di Marco S, Roberts R, Green N, Berrie E, Ishizuka AS, Nielsen CM, Bardelli M, Partey FD, Ofori MF, Barfod L, Wambua J, Murungi LM, Osier FH, Biswas S, McCarthy JS, Minassian AM, Ashfield R, Viebig NK, Nugent FL, Douglas AD, Vekemans J, Wright GJ, Faust SN, Hill AV, Long CA, Lawrie AM, Draper SJ. Human vaccination against RH5 induces neutralizing antimalarial antibodies that inhibit RH5 invasion complex interactions. JCI Insight. 2017 Nov 2;2(21). pii: 96381. doi: 10.1172/jci.insight.96381. PMID: 29093263

Sumi Biswas presented "Development of transmission-blocking malaria vaccine" on 12 January 2017, Edinburgh, UK

Sumi Biswas presented "Development of transmission-blocking malaria vaccine" on 18 January 2017, London, UK

Simon Draper presented "Development of a broadly-neutralising vaccine against blood-stage *P. falciparum*" on 12 April 2017, Arnhem, Netherlands

Navin Venkatraman presented "Safety, immunogenicity and durability of a novel malaria vaccine candidate, R21 adjuvanted with Matrix-MTM" on 22-25 April 2017, in Vienna, Austria

Navin Venkatraman presented "Safety, immunogenicity and durability of a novel malaria vaccine candidate, R21 adjuvanted with $AS01_B$" at the ASTMH 66th Annual Meeting, 05-09 November, Baltimore, USA

Navin Venkatraman presented "High level efficacy in humans of a next-generation *Plasmodium falciparum* anti-sporozoite vaccine: R21 in Matrix MTM adjuvant" at the ASTMH 66th Annual Meeting, 05-09 November, Baltimore, USA

The MultiMalVax project was also presented at various other occasions.

Leishmaniasis vaccines

The leishmaniases are one of the world's most neglected diseases, affecting largely the poorest of the poor, mainly in developing countries, and presenting a severe barrier to socio-economic development.

The leishmaniases are caused by protozoan parasites from more than twenty *Leishmania* species. These parasites are transmitted to humans by the bites of the infected female phlebotomine sand-fly. There are three main forms of leishmaniasis: cutaneous leishmaniasis (CL), visceral leishmaniasis (VL, also known as kala-azar), and mucocutaneous leishmaniasis (MCL). Whereas cutaneous and mucocutaneous leishmaniases are chronic and non-life-threatening, visceral leishmaniasis is responsible for over 20,000 deaths per year. The organ site and the severity of the disease depend on the *Leishmania* species, the host immune status and the response capacity of the infected individual[3 4]. Between 20 to 60% (depending on geographical location) of visceral leischmaniasis patients develop a syndrome known as post kala-azar dermal leishmaniasis (PKDL), a severe and chronic form of cutaneous leishmaniasis that usually develops after treatment for VL caused by *L. donovani*, but which can occur in the absence of previous VL or concomitant with VL therapy.

According to the most recent reports by WHO and CDC, leishmaniases affects people in nearly 88 developing and developed countries where about 350 million people are living in these regions. The disease is reported in approximately 12 million people worldwide with recorded incidence of 1.5-2 million new cases each year of cutaneous form and 500,000 new cases of the visceral form of the disease. Collectively, approximately 2.4M disability-adjusted life years (DALY) are lost to the leishmaniases.

Current treatment for leishmaniases is limited to few drugs characterised by high costs, significant adverse events and, in some cases, increasing parasite drug resistance[35]. Visceral leishmaniasis always requires treatment. Commonly used medicines include sodium stibogluconate (Pentostam), amphotericin B, paromomycin, and miltefosine. Cutaneous leishmaniasis will often heal without treatment. However, treatment can speed healing, reduce scarring, and decrease risk of further disease. Lesions caused by mucocutaneous leishmaniasis are normally treated with amphotericin B and paromomycin.

There is no licensed vaccine against any form of human leishmaniasis. As recovery from infection is usually accompanied by strong immunity and as it is possible to protect experimental animals against live challenge or with subunit vaccines, hope for developing a vaccine for humans has always been strong. *Leishmania* vaccine development has proven to be a difficult and challenging task, which is mostly hampered by inadequate knowledge of parasite pathogenesis and the complexity of immune responses needed for protection. So far, preventative measures are restricted to vector control with insecticides-treated bed nets and indoor residual spray.

34. Kaye, P and Scott, P, Nature Rewies. Microbiology 2011;9:604-615
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LEISHDNAVAX

The GHIT-funded project LEISHDNAVAX started in October 2017 and has an overall budget of ¥ 409,666,429 or approximately €3.1M. The project aims at completing the preclinical development of a novel T cell epitope-enriched DNA vaccine candidate for leishmaniases.

PARTNERS

- Mologen AG, Germany
- University of Nagasaki, Japan
- Charité - Universitätsmedizin Berlin, Germany
- London School of Hygiene and Tropical Medicine (LSHTM)

This vaccine has already been successfully tested for antigenicity in humans in *ex vivo* studies, and for immunogenicity and efficacy in a mouse model for visceral leishmaniasis. LEISHDNAVAX is a pentavalent DNA vaccine candidate against leishmaniases coding for optimised and T cell epitope-enriched variants of the *Leishmania* antigens kmp-11, TSA, elongation factor P74, and cysteine proteases CPA and CPB[36]. These antigens were selected according to the following criteria: i) no significant similarity to human proteins; ii) conserved among the different *Leishmania* species pathogenic in humans, in different *Leishmania*-endemic regions and over extended time spans, iii) known to be immunogenic and to induce human CD4+ and CD8+ T cell responses in different endemic populations; iv) rich in T cell epitopes in particular in the conserved sequence stretches; and v) expressed in promastigote and amastigote forms of the parasite[?].

MAIN OBJECTIVES

1. Preclinical evaluation of the vaccine candidate to study the protection against cutaneous leishmaniasis
2. Preclinical evaluation of the vaccine candidate to study its therapeutic potential against cutaneous leishmaniasis
3. GMP production and clinical batch release
4. Preparation of a phase I clinical trial to assess the safety and immunogenicity of the vaccine candidate in humans.

Preclinical, process development, production, IMPD

Preparation of the mouse experiments at the University of Nagasaki to assess the protective effect of the LEISHDNAVAX vaccine candidate against cutaneous leishmaniasis have started. Prophylactic vaccine efficacy will be evaluated in different strains of mice including C57BL/6J and BALB/cJ mice. Different species of *Leishmania* will be tested, whose antigens have already been defined and included into the vaccine design[36], and for which mouse models of infection have already been established. Different immunisation schemes will be tested to determine the number of the immunisations that can induce protective immunity against *Leishmania* infection. Dosages will be based on data from previous mouse immunisation studies[36].

Production of the preclinical and clinical batches of the DNA vaccine candidate (the individual MIDGE vectors) will be subcontracted by Mologen to a Contract Manufacturing Organisation (CMO) to be selected at the beginning of the project activities. Release of the GMP clinical batch is planned for 2019.

The design/preparation of the peptide libraries and the generation of the protein antigens to assess the immunogenicity of the vaccine candidate in the mouse model have started at Charité - Universitätsmedizin Berlin.

Delivery Platform, Adjuvants and Viral Vectors

The DNA vaccine candidate tested by the consortium uses a Minimalistic Immunogenically Defined Gene Expression (MIDGE) vector[37]. They are linear double-stranded DNA molecules, only containing the antigens-coding sequences, promoter and poly-adenylation site, but no bacterial plasmid backbone sequences that have been shown to reduce transgene expression and immunogenicity[38],[39]. MIDGE vectors are stabilised against exonucleases by terminal looping or L-nucleotides. Biodistribution and toxicity data for MIDGE vectors have recently been published[40],[41] and document an excellent safety profile.

Clinical Development

Preparation of a phase I clinical trial to assess safety and immunogenicity of the LEISHDNAVAX candidate will be undertaken by the project partners. Scientific advice by the competent authorities will be sought for the preparation of the clinical trial protocol and the Investigational Medicinal Product Dossier (IMPD). SOPs will be developed for the preparation, cryopreservation, storage and transport of the clinical samples as well as for assessing the immunological responses to the vaccination.

36. Das S *et al*, Sci Transl Med. 2014;6:234ra56
37. Moreno S *et al*, Vaccine. 2004;22:1709-16
38. Chen ZY *et al*, Mol Ther. 2008;16:548-56.
39. Dietz WM *et al*, Mol Ther. 2013;21:1526-35.
40. Galling N *et al*, Hum Gene Ther Methods. 2012;23:264-70.
41. Endmann A *et al*, Vaccine. 2014;32:3460-7.

Viral vaccines

In addition to the work outlined above on vaccines against major human parasites in which EVI is actively involved, EVI has become increasingly interested and engaged in the development of vaccines against viruses causing diseases of poverty or emerging diseases. Viruses are small infectious agents that can only replicate inside the living cells of other organisms. Although far less complex than other microorganisms, the development of vaccines against some viruses causing serious human disease nevertheless can present a formidable challenge.

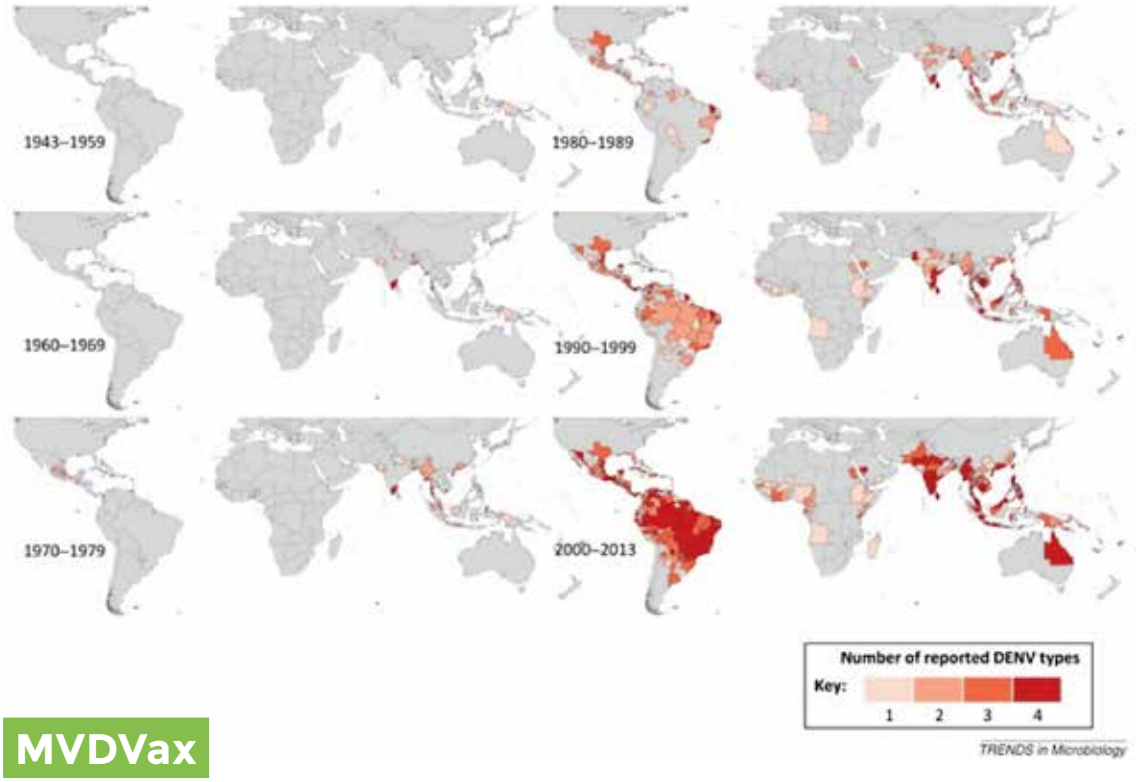
Dengue vaccine

Dengue fever is an arbovirus transmitted by *Aedes mosquitoes*. Despite the severity of the illness, it is seldom lethal. Dengue virus (DENV) is a single positive-stranded RNA virus of the family of *Flavivirus*. Classically, four serotypes of the virus are currently described and all of them are responsible of the disease. These four virus groups however show as much antigenic distance within a group as between groups, explaining why dengue is provoking so highly variable immune responses[42]. This is the biggest challenge for dengue vaccine development.

The disease is endemic in more than 100 countries with an estimate of 390 million dengue virus infections annually, of which 96 million show clinical manifestations with about 500,000 hospitalizations. Dengue is estimated to cause 20,000 deaths every year, mainly among children. Although mortality is lower compared to other tropical infectious diseases such as malaria, the scale of human suffering and the resources invested in the control of dengue make it a major global health problem[43]. Dengue viruses are spreading rapidly and in the last decade outbreaks have occurred in Africa[44].

The current licenced vaccine Dengvaxia® which has been approved in Mexico, The Philippines, Brazil, El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand and Singapore does not provide equal protection against all four known dengue serotypes. After review of the safety data, it was decided to exclude those aged 6–8 years due to an excess of hospitalisation related to dengue illness, and start the indicated age range at 9 years[45]. Other candidates currently in preclinical or clinical development also focus on B-cell response and are predicted to encounter similar problems leading to the risk of limited protection against specific serotypes and of the so-called dengue viral interference problem: sequential infections with different dengue serotypes can increase the risk of developing a severe and potentially lethal disease due to an antibody enhanced disease phenotype. Besides Dengvaxia®, two other vaccine candidates entered phase III clinical trials in 2016: the live-attenuated tetravalent dengue vaccine candidate TAK-003 from Takeda and the tetravalent live-attenuated lyophilised vaccine from Butantan Institute.

42. Dengue viruses cluster antigenically but not as discrete serotypes. Leah C. Katzelnick &al. Science18 Sep 2015 : 1338-1343
43. http://www.who.int/mediacentre/factsheets/fs117/en/
44. Global spread of dengue virus types: mapping the 70 year history. Messina, Jane P. *et al.* Trends in Microbiology , Volume 22 , Issue 3 , 138 - 146
45. Dengue vaccine: WHO position paper – July 2016.. Wkly Epidemiol Rec. 2016 Jul 29;91(30):349-64. http://www.who.int/wer/2016/wer9130.pdf?ua=1 (accessed 29-05-2017)



MVDVax

MVDVax is a GHIT-funded project with a budget of ¥61,290,240 or approximately €0.5M, which commenced in October 2015 and finished in March 2017.

The aim of the current project stage is to demonstrate the proof-of concept of a measles-virus-dengue vaccine candidate (MVDVax) in a non-human primate model, to produce all the data required for follow-up projects, and to be ready for GMP production, toxicology studies and clinical trials.

MVDVax target populations are primarily children and adults in dengue-endemic regions and travellers to affected areas. MVDVax overcomes the lack of equal protection provided by current vaccine candidates against different serotypes by using a single vector live dengue vaccine, allowing the more balanced and controlled expression of the tetravalent antigens representing different serotypes. Furthermore, MVDVax focuses on T cell responses by expressing a mixture of non-structured protein regions, which show stronger T cell response compared to structured dengue proteins, but are missing from almost all dengue vaccines in development (except live attenuated dengue virus). In addition, MVDVax uses only part of the E-protein, avoiding regions suspected to induce antibody-enhancing phenotypes and allowing for a smaller vector insert. Because MVDVax uses the measles virus as a way to express the dengue antigens, it reduces the cost of production to that of the measles vaccine cost, which is appropriate for a disease of poverty.

PARTNERS

- European Vaccine Initiative (EVI), Germany
- Institut Pasteur Paris (IPP), France
- Institute of Tropical Medicine Nagasaki University (NEKKEN), Japan

RECENT ACHIEVEMENTS An optimised immunisation protocol for NHP vaccination was developed (3 doses, 0, 12 weeks, 23 weeks). All NHP showed seroconversion and good antibody titres against all four different Dengue serotypes were detected. While a T cell response was not directly observable after the single vaccination steps, a T cell response against the non-structured peptides was observed after challenge in MVDVax vaccinated animals but not in the Measles vaccinated control group. The antibody results looked very promising but did not predict the protection. The NHP were not protected from Dengue upon challenge and showed viremia as determined by qPCR. A lower viral load was observed on day 2, correlating with a reduced infectious viremia, which is most likely partially due to delay in viremia onset.

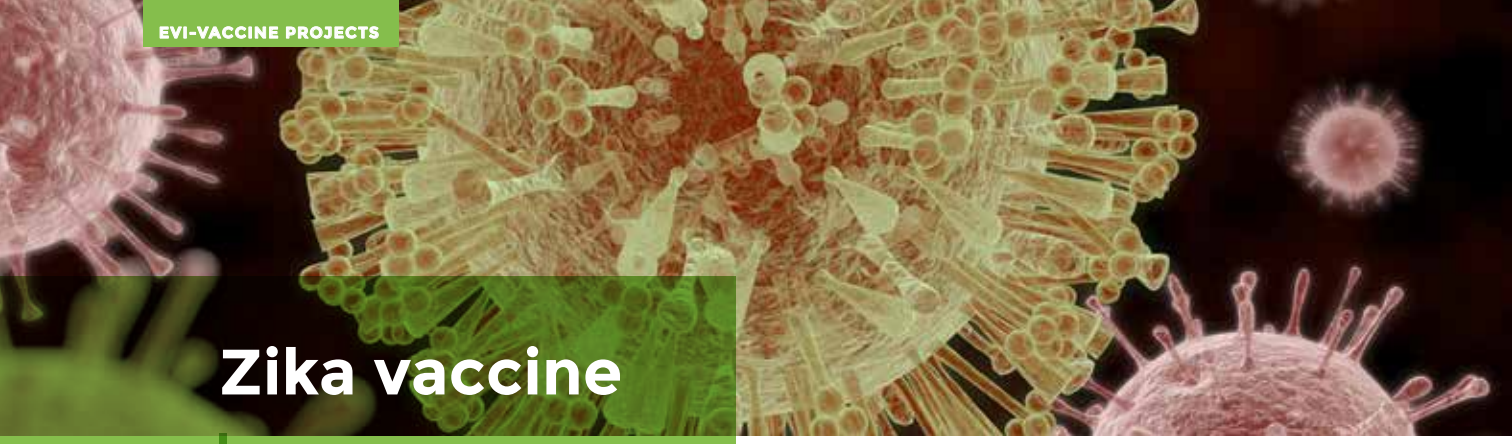
MVDVax

Preclinical, process development, production, IMPD

The stability of the MVDVax vector and stable EDIII expression across different vector batches was demonstrated.

Delivery Platform, Adjuvants and Viral Vectors

Measles virus is used as a vector to express the immunogenic dengue antigens.



Zika vaccine

Zika virus infection is a vector borne disease which recently has called the attention of the international community due to a large outbreak that started in 2015 and affected more than 70 countries and territories[46].

The recent rapid spread of the Zika virus in previously unaffected regions has provided strong epidemiological evidence that infection with this virus might be associated with neurological complications in adults and with an increase in severe congenital brain and central nervous systems malformations of newborns, the congenital Zika syndrome.

Disease

Zika virus is transmitted through the bite of an infected mosquito from the Aedes genus, mainly *Aedes aegypti* in tropical regions. The same mosquito also transmits the viruses causing dengue, chikungunya and yellow fever. The symptoms are similar to other arbovirus infections, and include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. These symptoms are usually mild and last for 2-7 days and often do not require any specific treatment. However, Zika virus infection during pregnancy was associated with congenital brain abnormalities, including microcephaly; and Zika virus was shown to be a trigger of the Guillain-Barré syndrome.

Epidemiology, burden & pandemic & epidemic preparedness

Zika virus is an emerging mosquito-borne flavivirus initially isolated from a rhesus monkey in the Zika forest in Uganda in 1947[47], [48]. The first human infection was reported in Nigeria in 1954[49]. Like dengue and chikungunya viruses, Zika virus adapted from an ancestral transmission cycle involving non-human primates and a broad spectrum of forest mosquito species as vectors to an urban cycle involving humans as reservoirs and the widely distributed *Aedes mosquitoes* as vectors[50]. Since the 1950s, Zika virus had only been reported as circulating sporadically in Africa and Southeast Asia. In 2007, Zika virus was isolated for the first time in the Pacific, on the Micronesian island of Yap[51]. Between October 2013 and April 2014, French Polynesia experienced the largest Zika outbreak ever reported at that time[52]. More than 32,000 patients were suspected for Zika virus infection. Between 2014 and 2015, Zika virus had spread to other Pacific islands, notably the Cook Islands and Easter Island (Chile). In March 2015, Brazil reported the autochthonous transmission of Zika virus[53] and declared an unprecedented outbreak six months later[54] with preliminary estimates of 440,000 to 1.3 million cases of infection through December 2015[55]. In February 2016, the WHO has declared the recent outbreak of the Zika virus a Public Health Emergency of International Concern, a declaration that was lifted by WHO in November 2016. Nevertheless, WHO indicated that Zika virus and associated consequences remain a significant public health challenge requiring intense action. In early 2017, 84 countries, territories or subnational areas with evidence of vector-borne Zika virus transmission were reported.

Control measures & prevention

There is no specific treatment or vaccine available against Zika virus. Preventive measures are centred on avoiding mosquito bites, reducing other forms of transmission (e.g. sexual transmission) and controlling the vector (mosquitos)[56]. These measures can, however, be challenging and have variable efficacy. Although disease symptoms are generally mild, the possible complications to pregnancy, new-borns and neurologic complications in adults, highlight the need of effective measures to prevent this disease. In this context, in March 2016, experts gathered at WHO agreed that the development of a preventive vaccine is a major priority to respond to Zika epidemics in the future[57].

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50. 2015; 386: 243–44
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53. Zanluca C *et al*, . Mem Inst Oswaldo Cruz 2015; 110: 569–72.
54. Dyer O, BMJ 2015; 351: h6983.
55. European Centre for Disease Prevention and Control, De- cember 10, 2015 (http:// ecdc.europa.eu/ en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf).
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Vaccine landscape

A Zika virus vaccine target product profile (TPP) for use in an emergency, or in a future outbreak scenario was developed jointly by WHO, UNICEF and a working group of independent experts in 2016 and revised in 2017[58],[59],[60]. WHO is currently developing a Zika vaccine development technology roadmap that states the vision and strategic goals for Zika vaccine development, based on input from developers, regulators and public health experts to identify the best way forward for the rapid, robust, safe, and evidence-based licensing of Zika virus vaccines. In 2017, the WHO convened a group of experts in a workshop on planning for Zika vaccine efficacy trials.

More than 40 Zika vaccine candidates are currently under development. According to WHO's Vaccine Pipeline Tracker, seven Zika virus vaccine candidates are currently in phase I and phase II clinical trials. These candidates are based on whole inactivated virus, or on the prME viral antigen using DNA, mRNA, peptide technologies, as well as on recombinant viral vectors. The measles vector based platform technology used in ZIKAVAX is built upon one of the safest and most efficacious vaccines available, the live attenuated measles vaccine. It has been demonstrated to be safe, with an efficacy rate of approximately 93% after one administration and 97% after 2 administrations. The measles vaccine induces a life-long immunity by efficiently stimulating long-lasting B- and T cells.

ZIKAVAX

ZIKAVAX is a collaborative project funded under the EU's H2020 Research and Innovation Programme and coordinated by EVI. This four-year project was initiated in October 2016 and has an overall budget of approximately €5M. The project is the joint effort of leading European experts from academia and industry with unique and specific technological expertise in viral vectors and vaccine development.

The ZIKAVAX project aims at developing a safe, effective, and affordable preventive vaccine against Zika virus infection. To achieve this goal, ZIKAVAX will use a delivery platform technology based on a measles vector with demonstrated proof of principle in humans and a preclinical track record of rapid adaptability and effectiveness for a variety of pathogens. In ZIKAVAX, following antigen selection and expression, immunisation studies will be conducted with the Zika vaccine candidate in mice and in a non-human primates challenge model that will be developed by the consortium. The ultimate goal of ZIKAVAX is the demonstration of safety and immunogenicity of a recombinant measles-Zika vaccine candidate (MV-ZIKA) in adult volunteers in a phase Ia clinical trial.

PARTNERS

- Commissariat à l'énergie atomique et aux énergies alternatives (CEA), France
- European Vaccine Initiative (EVI), Germany
- Institut Pasteur, France
- Themis Bio, Austria

RECENT ACHIEVEMENTS More than 40 different vaccine constructs were cloned and characterised in HEK293 cells. Based on the data, three constructs were selected for further immunogenicity and efficacy studies in mice. Additionally, a non-human primate challenge model for Zika virus infection was established at CEA.

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Preclinical, process development, production, IMPD

Institut Pasteur has initiated to work on the various Zika virus antigens. The sequences of these antigens were amplified from the Zika virus strain isolated from the ongoing outbreak in Brazil. The sequences are codon optimised and adapted to measles vector cloning. Several constructs have been generated and the expression level of the selected antigens is currently being evaluated in HEK293 cells. The antigen sequences were cloned into the measles vaccine vector in different transcription units, according to the desired level of expression. After sequencing of the measles vector plasmids expressing the different Zika antigens, replicating recombinant vectors were generated by reverse genetics using a cell-based system developed by Institut Pasteur and were further characterised for antigen expression, growth characteristics and genetic stability. Immunogenicity and efficacy evaluation of the MV-Zika vaccine candidates started in 2017 with availability of the data in 2018.

To demonstrate preclinical immunogenicity and protective efficacy of the recombinant MV-Zika vaccine candidate(s) in non-human primates, CEA established a non-human primate challenge model for Zika virus infection. Different doses of Zika virus inoculated subcutaneously were tested to infect non-human primates. All animals were infected as shown by PCR on viral DNA in the plasma and, upon re-challenge, full protection was achieved. Further analysis is on-going to define the clinical, immunological and virological endpoints that will be used to assess the effectiveness of the ZIKAVAX vaccine candidate(s).

Profiting from the knowledge acquired on manufacturing its MV-based Chikungunya vaccine candidate (MV-CHIK) currently in phase II clinical trial, Themis has already started the work to adapt and optimise the upstream and downstream processes previously established. The GMP manufacture of the selected MV-Zika vaccine candidate is envisaged for mid-2018.

Delivery Platform, Adjuvants and Viral Vectors

For the fast track development of the envisaged Zika virus vaccine, the live attenuated measles vaccine, one of the safest and most efficacious vaccines available, will be used as a delivery vector for Zika virus protective antigens.

This delivery platform technology consists of a genetically modified live attenuated measles virus (Schwarz strain) that allows expression of heterologous antigens. Antigens of different arboviruses such as Chikungunya, Dengue or West Nile virus have already been successfully inserted into the measles vaccine vector and their strong immunogenicity or protective capacity has been established in preclinical and clinical studies, also in the presence of pre-existing immunity to the vector[61],[62],[63],[64].

The manufacturing process for these MV-based vaccines has been optimised to give higher yields and purity than the standard measles vaccine manufacturing process. It uses standard equipment and lends itself to further scale up as well as technology transfer to low and middle income countries, thus ensuring the timely availability of a preventive vaccine whenever a new epidemic occurs.

Clinical Development

A phase I clinical trial is planned to be conducted in 2019/2020 in Europe.

Harmonisation

The ZIKAVAX consortium will actively interact with other European networks working on Zika virus infection (e.g. ZIKAlliance, ZikaPLAN and ZIKaction) to help filling the knowledge gaps on Zika infection, epidemiology, and pathogenesis and to investigate options for treatment and prevention. CEA is also a partner of the ZIKAlliance EU-funded project and will facilitate networking activities with this consortium.

Outreach and Communication

Odile Leroy presented “Zika virus and other mosquito-borne viruses” at the B-Debate meeting on 23-24 May 2017, Barcelona.

Odile Leroy was invited to the 18th DCVMN annual general meeting on 25-28 Sep 2017, Seoul to present the ZIKAVAX activities.

Odile was invited by Themis as a panellist in a symposium “New Horizons for making and regulating” on 13-14 Sep 2017 in Vienna.

61. Ramsauer, Lancet Inf. Dis 15:519, 2015
62. Brandler, J Infect Dis 206:212, 2012
63. Brandler, Vaccine 28:6730, 2010
64. Escriou, Virology 452-453:32, 2014

Universal influenza vaccine

Influenza, also called flu, is a major viral respiratory disease in mammals and birds caused by influenza viruses. It can cause mild to severe illness. In human, serious outcomes of flu infection can result in hospitalization or death. Pneumonia, bronchitis, sinus infections and ear infections are examples of flu-related complications.

pidemiology, burden

Some people are at higher risk of serious flu complications such as pregnant women, children under 5 years, adults aged 65 years and people with medical conditions. Health care workers are at higher risk of contracting influenza due to increased exposure to infected patients.

The disease occurs yearly as outbreaks, resulting in about three to five million cases of severe illness and about 290,000 to 6500,000 deaths (http://www.who.int/mediacentre/factsheets/fs211/en/). Influenza is a seasonal disease occurring mainly in winter in the temperate zone of the northern and southern hemisphere and at any time of the year in the areas in the tropics. Influenza-associated mortality rates are higher in low-income countries mainly due to lack of access to adequate medical care, limited public health infrastructures, social factors, housing conditions and population density. Larger outbreaks due to novel emerging influenza virus strains are known as pandemics and can result in the death of million people.

The virus is spread by aerosol transmission and the incubation period is about 2 days.

Control measures

The major effective control measure for preventing infection and illness is the vaccination. Anti-viral treatment are available for patients with severe disease. However, the disadvantage of some anti-viral agents is the rapid development of resistance.

Prevention

Vaccination is the most effective way to prevent infection and severe outcomes caused by influenza viruses.

Vaccine landscape

Current vaccines either consist of inactivated viruses grown in chicken eggs, live attenuated viruses or recombinant hemagglutinin. As influenza viruses undergo continuous antigenic changes, the current vaccines provide only limited protection against new epidemic or pandemic viruses. The seasonal influenza vaccines composition has to be updated each year and therefore vaccines need to be administered annually. As a consequence, continuous monitoring and selection of viruses, as well as production of vaccines are necessary each year. A major limitation is therefore that the relatively long manufacturing and production time results in a vaccine that does not always contain the correct viruses to match the epidemic strains circulating in the community. Moreover these vaccines are less or not at all affordable for low and middle-income countries.

A significant advance would be the development of a new generation of influenza vaccines that stimulate production of a robust, broadly neutralising immune response, not only to drifted variants of seasonal influenza viruses, but preferably also to potential pandemic strains. In addition “universal” influenza vaccines, that do not require annual immunisation, may be the best option for low and middle income countries, including those in subtropical and tropical regions, to decrease the burden of disease.

EDUFLUVAC

In order to address the problem of antigenic drift and annual vaccine reformulation, the EU FP7 EDUcate inFLUenza VACcine (EDUFLUVAC) consortium proposed the development of a novel influenza vaccine encompassing a combination of multiple influenza haemagglutinin (HA) or neuraminidase (NA) antigenic variants within a single subtype.

The innovation of this approach lies in the selection of antigenic variants with maximal sequence diversity (each (sub)type is addressed separately), resulting in diluted strain-specific epitopes and enhanced presentation of common epitopes to the immune system, thereby increasing the breadth of the antibody response. Since, by this approach, the relative concentration of common influenza epitopes is increased while that of strain-specific epitopes is decreased, the immune system is expected to learn what "the common characters" of influenza viruses are. This approach builds on the concept of the Epitope Dilution Phenomenon, developed by Ed Remarque at BPRC, as a practical strategy for the induction of broad, cross-variant antibody responses against polymorphic antigens. The consortium expressed the selected HA components representing antigenic drift variants within the H1, H3, and B influenza viruses as virus-like particles (VLPs) using the insect cells-baculovirus expression system. The VLP antigen expression system helps cross-linking B cell receptors and boosting humoral immune responses.

PARTNERS

- Biomedical Primate Research Centre (BPRC), The Netherlands
- ETNA BIOTECH s.r.l., Italy
- European Vaccine Initiative (EVI), Germany
- Instituto de Biologia Experimental e Tecnológica (iBET), Portugal
- National Institute for Biological Standards and Control (NIBSC), a centre of the Medicines and Healthcare Products Regulatory Agency, United Kingdom
- Redbiotec AG, Switzerland
- Wageningen Bioveterinary Research (WBVR), The Netherlands

The EDUFLUVAC project started in November 2013 with a budget of €4,6M and was concluded in October 2017. This collaboration included seven renowned organisations from Europe, including two research intensive Small and Medium Enterprises (SMEs), with longstanding experience in antigen discovery, pre-clinical evaluation, product development and regulatory issues.

RECENT ACHIEVEMENTS The main achievements in 2017 were:

- completion of proof-of-concept studies in ferrets and non-human primates.
- organisation of a successful work-shop entitled: "Four years of European research on the development of universal influenza vaccines: what have we learnt and how can we move forward?".

Preclinical, process development, production, IMPD

To define which strains would represent an appropriate coverage within one (sub)type, five HA antigens were selected for each of the H1, H3 and B (sub)types based on sequence diversity and serological cross-reactivity; the selected strains represent major antigenic drift groups in each (sub)type. Concomitantly, three NA antigens from the N1 subtype and six HA antigens from Group 2 subtypes were selected by similar criteria.

The selected HA and NA sequences were assembled into baculovirus expression vectors using the rePAX® technology of Redbiotec. Production of target VLPs were successfully completed at iBET. Upstream and downstream process optimisation was undertaken at iBET to generate a VLP production platform suitable for GMP production. Several potential batch release assays have been implemented and additional analytical techniques for VLPs monitoring during production and purification processes, and for rational process optimisation were also developed.

All mouse immunisation studies were completed and sera were analysed by quantitative ELISA at ETNA Biotech and also by Microneutralisation Assay (MN) performed at NIBSC. The MN assay is the main decision making assay, measuring the ability of sera to neutralise both homologous and heterologous influenza viruses, for further antigen down-selection. Competitive ELISA has also started to provide insights into the mechanisms and demonstrate the broadening of the antibody response. Mouse immunogenicity studies show that for the H3 and B strains the response was broadened beyond the vaccine composition, i.e. strains isolated 10 years after the last strain in the vaccine composition are neutralised by pentavalent VLP immunised mouse sera. The H3N2 and B strain data show that at least five components on a single VLP induce broadened responses. Based on the mouse immunogenicity data, challenge studies in ferrets and non-human primates to provide proof of concept of the EDUFLUVAC project were conducted at WBVR and BPRC respectively. Challenge studies with the pentavalent H1 VLPs in both ferrets and non-human primates did not induce a broadening of the humoral or cellular immune responses to the heterologous challenge virus A/California/04/2009 (H1N1)pdm09 and also did not lead to protection after challenge. In contrast, vaccination of ferrets with either a mixture of monovalent H3 VLPs or the pentavalent H3 VLPs induced a serological and cellular immune response against heterologous H3N2 strain and led to reduction in clinical severity and a lower virus load after challenge.

•••

Delivery Platform, Adjuvants and Viral Vectors

The EDUFLUVAC project uses VLPs to deliver multiple influenza HA and/or NA antigenic variants. Following careful selection of the antigen strains, assembly in baculovirus vectors and VLP production in insect cell lines was completed at Redbiotec and at iBET, respectively.

Capacity strengthening, Workshops, Training

During 2017 one master student and one PhD students continued their work at iBET on the EDUFLUVAC project supporting the upstream and downstream processes for influenza VLP production:

• Sofia Carvalho (PhD student): her work was mainly related to setting-up specific in-process techniques to monitor and improve purification of influenza VLPs. Her PhD thesis will be defended in 2018.

• Daniela Sequeira (Master student): her work at iBET focused on analysing the versatility of insect cells for the production of influenza VLPs. Daniela defended her Master thesis in 2017. Title: Exploring insect cells versatility for production of Influenza VLPs.

EDUFLUVAC workshop "Four years of European research on the development of universal influenza vaccines: what have we learnt and how can we move forward?".

In the series of workshops organised by the EDUFLUVAC consortium, the third and last workshop took place in Brussels on 12-13 June 2017 and was entitled: "Four years of European research on the development of universal influenza vaccines: what have we learnt and how can we move forward?". The aim of this workshop was to bring together the five consortia that received funds by the EC FP7 programme in 2013 and to discuss what has been achieved, how the activities can be continued in the future after the projects come to an end and how to strengthen the European vaccine development landscape. This workshop has been a great opportunity for the five consortia to discuss the products and technologies developed, and to present the results of their research to stakeholders and several funding organisations.

The vaccine development pipeline in Europe is well populated with promising vaccine candidates from the preclinical stage all the way to comparative proof-of-concept clinical trials. Furthermore, the five EU consortia have developed successful technology platforms, to allow smooth process development and GMP production, and have created an efficient clinical development infrastructure.

The European influenza community agreed that building on the existing consortia and knowledge generated by creating a common portfolio management would greatly increase the chance of success to bring the products further into the pipeline of vaccine development. The community will have to work together to:

• Define the Preferred Product Characteristics for broadly reactive influenza vaccines

• Agree on the go-no go criteria for selecting, assessing and advancing vaccine candidates

• Propose a regulatory and clinical strategy

• Put in place harmonization efforts (standards and assays) as well as comparative platforms.

Harmonisation

The EDUFLUVAC consortium partners' iBET and NIBSC continued their collaboration to develop a method for the quantification of multiple HA in influenza VLPs by isotope dilution mass spectrometry. Their collaborative work will continue also after the end of the project.

Outreach and Communication

The following presentations were given by the EDUFLUVAC partners during this reporting period:

Sofia Carvalho (iBET, Portugal) presented "Monitoring and improving influenza Virus-like particles downstream processing using a click chemistry approach" at the ISPPP 2016 meeting, 06-09 November 2016, Salzburg, Austria.

Gerrit Koopman (BPRC, The Netherlands) presented "Diversity Covering approach for universal influenza vaccines: the EDUFLUVAC EC-FP7 Project" at the EVI Rendez-Vous, 14 December 2016, Paris, France.

Sofia Carvalho (iBET, Portugal) presented "Challenges in influenza virus-like particles production: New analytical tools and downstream process optimization" at the Influenza Vaccine for the World Conference, 19-21 April 2017, Lausanne, Switzerland.

Antonio Roldão (iBET, Portugal) presented "A modular strategy for multi-HA influenza VLPs production: combining stable and baculovirus-mediated expression in insect cells" at 25th ESACT, Lausanne, Switzerland, 14-17 May 2017.

Ricardo Correia (iBET, Portugal) presented "Adaptive Evolutionary Engineering of Insect cells for Improved Influenza HA VLPs Production" at 25th ESACT, Lausanne, Switzerland, 14-17 May 2017.

Odile Leroy (EVI, Germany), Edmond Remarque (BPRC, The Netherlands), Gerrit Koopman (BPRC, The Netherlands) and Antonio Roldao (iBET, Portugal) presented the EDUFLUVAC project and its main achievements at the third EDUFLUVAC workshop "Four years of European research on the development of universal influenza vaccines: what have we learnt and how can we move forward?", 12-13 June 2017, Brussels, Belgium.

Odile Leroy (EVI, Germany) presented the EDUFLUVAC project at the workshop organised by the European Commission on the development of broadly reactive universal flu vaccines, 14 June 2017, Brussels, Belgium.

Sofia Carvalho (iBET, Portugal) presented "Challenges in Influenza virus-like particles: new analytical tools and downstream process optimization" at the Influenza Vaccines for the World meeting, 19-21 April 2017, Lausanne, Switzerland.

Sofia Carvalho (iBET, Portugal) presented "Production and purification of influenza virus-like particles using single-use technologies" at the Single-use Technologies II: Bridging Polymer Science to Biotechnology Applications meeting, 07-10 May 2017, Tomar, Portugal.

Cristina Peixoto (iBET, Portugal) presented "Improving purification of influenza virus-like particles using a pseudo-affinity strategy" at the Affinity 2017 meeting, Paris, France, 26-29 June 2017.

Sofia Carvalho (iBET, Portugal) presented "Improving Downstream Processing of Influenza Virus-like Particles using Multi-column Chromatography" at the PREP 2017 meeting, Philadelphia, USA, 16-19 July 2017.

Paula Alves (iBET, Portugal) presented "Bioprocess Engineering of Insect cells for Accelerating Vaccines Development" at the Biochemical and Molecular Engineering XX meeting, Newport Beach, CA, USA, 16-20 July 2017.

Cristina Peixoto (iBET, Portugal) presented "Novel Pseudo-affinity Strategy for the Purification of Influenza Virus-like Particles" at the ISPP 2017 meeting, Philadelphia, USA, 19-21 July 2017.

Ricardo Silva (iBET, Portugal) presented "Multi-column chromatographic purification of influenza virus-like particles" at ICB2017, Cascais, Portugal, 17-21 September 2017.

Antonio Roldão (iBET, Portugal) presented "Bioprocess engineering of insect cells for accelerating vaccines development" at 9th Annual PEGS Europe Summit, Lisbon, Portugal, 16 November 2017.

OTHMAR G ENGELHARDT

Dr Othmar G Engelhardt is a Principal Scientist in the Division of Virology of the National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare products Regulatory Agency in the UK.

His lab is a WHO Essential Regulatory Laboratory (ERL) within GISRS (Global Influenza Surveillance and Response System); in this role, his team produces reference reagents for the potency testing of inactivated influenza vaccines and advises WHO on various vaccine-related matters, including the biannual WHO influenza vaccine composition recommendations. His laboratory conducts influenza virus research at different levels of biocontainment and has access to a SAPO4 facility that is required in the UK to work with wild-type highly pathogenic avian influenza viruses.

His research focuses on the improvement of candidate vaccine viruses and potency testing of influenza vaccines, on the standardisation of influenza serology assays and assessment of new vaccine concepts.

Recently, his lab has branched out to respiratory syncytial virus (RSV), and established the first international standard for antibody to RSV.

Outside of work, he enjoys running, rock climbing and exploring the beautiful countryside of his adopted home country, the United Kingdom, and of other countries. If he lived near mountains, he would be found skiing every winter. He is also a keen baker and always interested in new recipes for delicious cakes.

His team was a partner in the EU-funded EDUFLUVAC project and conducted serologic analyses of pilot and preclinical studies performed by other partners.

He says about the EDUFLUVAC project: *'I was really impressed by the collaborative spirit of the consortium –everybody worked together towards the aims of the project, with open communication at all stages. The work plans were adjusted flexibly to reflect results obtained; thus, the consortium delivered a challenging project in the timelines given by the grant and laid the groundwork for a very interesting, new vaccine concept. I would love to continue work with this group of scientists; there is real potential, both in the vaccine concept and in the combined expertise of the consortium.'*

VACCINE BATCH TO VACCINE BATCH COMPARISON
by consistency testing

VAC2VAC

The overall objective of VAC2VAC is to demonstrate proof of concept of the consistency approach for batch release testing of established vaccines. This means that animal-free assays instead of animal tests shall be used to ensure that each vaccine batch produced nowadays is consistent with a batch already proven to be safe and efficacious in registration studies. Hence the name "consistency approach". It covers vaccine potency, safety and animal welfare. Due to the nature of the animal-free assays, the consistency approach also clearly will speed up the release time so that vaccine batches will be available for vaccination much quicker.

The project's first objective is to develop, optimise and evaluate non-animal methods to demonstrate that the critical quality attributes of each vaccine batch remains consistent. Methods will be developed that can be used to test several types of human and/or veterinary vaccines currently on the market as well as for different adjuvants that are included in some vaccine formulations to enhance the immune response.

The project's second objective is to work with regulatory authorities to develop guidance for regulatory approval and implementation of the newly developed methods.

The three main steps to reach these objectives are:

1. Development of new or optimisation of existing non-animal methods for consistency testing

This is the core activity of the project, with a focus on development and optimisation of physicochemical methods, immunochemical methods, cell-based assays, and multi-parametric assays & bioinformatics. All these activities will focus on non-animal methods that can be applied at different stages throughout the production process, including the formulated drug product where possible. The human and veterinary vaccines included in VAC2VAC were selected based on the number of the animals currently used for vaccine quality and safety testing, the severity of the currently used animal test or, in some cases, as models for complex adjuvants that are difficult to characterise with existing methods.

2. Pre-validation of selected methods

For selected methods developed in VAC2VAC, small-scale multi-centre studies will be set up to assess the transferability and inter-laboratory reproducibility of the methods.

PARTNERS

- Biomedical Primate Research Centre (BPRC), The Netherlands
- Boehringer Ingelheim (BI), Germany
- College ter Beoordeling van Geneesmiddelen (CBG/MEB), The Netherlands
- European Commission, Joint Research Centre (JRC) Italy
- European Vaccine Initiative (EVI), Germany
- GSK Biologicals (GSKBio), Belgium
- Institute for Translational Vaccinology (Intravacc), The Netherlands
- International Alliance for Biological Standardization for Europe (IABS-EU), France
- Istituto Superiore di Sanità (ISS). Italy
- Merck Sharp & Dohme (MSD), The Netherlands
- Merial (Merial), France
- National Institute for Biological Standards and Control (DH-NIBSC), United Kingdom
- National Institute for Public Health and the Environment (RIVM), The Netherlands
- Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH (Austrian Agency for Health and Food Safety: AGES), Austria
- Paul-Ehrlich Institute (PEI), Germany
- Sanofi Pasteur (SP), France
- Scientific Institute of Public Health (WIV-ISP), Belgium
- University Medical Center Groningen (UMCG), The Netherlands
- University of Applied Sciences Utrecht (HU), The Netherlands
- University of Utrecht (UU), The Netherlands
- Zoetis Belgium SA (Zoetis), Belgium

Methods that are successful in these pre-validation studies and that are proposed for inclusion in regulatory monographs, will be submitted to the EDQM Biological Standardisation Programme to be considered for further validation studies.

3. Regulatory acceptance of the consistency approach

To maximise the chances of regulatory acceptance and implementation of the consistency approach for batch release, the development of methods in VAC2VAC will involve close cooperation between public partners and industry partners in consultation with the regulatory bodies and VAC2VAC Scientific and Ethics Advisory Committee (SEAC).

RECENT ACHIEVEMENTS A system for the management of samples and reagents was developed (including a database of all sample requests/status and a log of all shipments) and multiple Material Transfer Agreements (MTAs) between VAC2VAC partners were agreed. This allowed for delivery of vaccine samples from Industry partners to Public partners and initiation of the laboratory work summarised below.

Physicochemical methods

The development of mass spectrometry assays for Leptospira and DTaP (Diphtheria, Tetanus, Pertussis) vaccines has started. The objective is to be able to quantify antigens in the complex vaccine which may contain multiple different components and sometimes adjuvant. Conformational fingerprinting (a technique that can be used to monitor vaccine quality based on the structure of the antigen) of the tetanus vaccines has also been initiated.

Immunochemical methods

Preliminary work has been started on the development and characterisation of monoclonal antibodies that will be used in the development of antigen content and quality assays for human and veterinary vaccines.

Cell based assays for consistency testing

The development of assays based on vaccine mediated activation of special reporter cell lines has started for the different antigens/vaccines.

Development of an antigen-specific antibody producing B-cell assay is ongoing for DTaP vaccines.

Work on the development of a safety test for tetanus vaccines has started by determining the sensitivity of the reporter cell line to tetanus toxin. In addition, preparatory work has started on the development of a cell-based assay for toxicity testing of veterinary *C. perfringens* C antigen.

Multiparametric assays and bioinformatics

The characterisation of *Clostridium tetani* seed strains has started. DNA sequencing, RNA sequencing and targeted proteomics have been used to characterise a seed strain for stable and reproducible production of toxin for human vaccines.

The development of an alternative pertussis vaccine safety test has been initiated with the goal of improving an existing cell-based assay to allow a fully quantitative readout.

COENRAAD HENDRIKSEN

Coenraad Hendriksen is emeritus professor at Utrecht University and scientific consultant to the Institute for Translational Vaccinology (Intravacc) in The Netherlands. He studied veterinary medicines and a post-doc training in laboratory animal science. During his professional life he worked at the National Institute for Public Health and the Environment (RIVM) and at Intravacc with a specific interest in model development in lot release testing of vaccines, particularly with the aim to refine, reduce or replace the use of laboratory animals. As such he has been involved in several interlaboratory validation studies organised by European Directorate for the Quality of Medicines and HealthCare (EDQM) and the European Centre for the Validation of Alternative Methods (EURL-ECVAM). At Utrecht University he was head of The Netherlands Centre for Alternatives to animal experimentation.

In his non-professional life he enjoys to work outside: being a hobby farmer, keeping sheep and chicken. In contrast he also likes to visit museums and to collect modern art.

He is part of Intravacc's team as partner in the IMI2-funded VAC2VAC project and is a member of the Scientific Management team.

He says about the VAC2VAC project: it is a great opportunity to work in a project which focus it is to improve the science behind the characterisation and evaluation of vaccine lots and which also aims to reduce significantly the use of laboratory animals for these purposes. The project is an interesting, but also challenging, a mix of partners: academia, research institutes, regulators and control authorities, vaccine related alliances and vaccine manufacturers. Most of all, I like the commitment of the consortium to face reality with the objective to change reality.

Development of platform technology for studying the interaction of vaccines/adjuvants with antigen presenting cells is ongoing for different antigens. The aim is to develop functional tests to evaluate adjuvant stability and/or to develop an *in vitro* potency test.

Work on 'Pre-validation of selected methods'

A template describing requirements for method development and validation has been developed and is now being revised based on comments received from the consortium partners.

Once implemented and completed by the testing laboratories, the template will help the consortium decide which methods should be prioritised for pre-validation and validation.

VAC2VAC

Harmonisation

VAC2VAC work package 5 organised a workshop involving 30 experts (VAC2VAC partners, EDQM, members of European Pharmacopoeia expert groups and of European Medicines Agency working groups) to discuss ways of optimising the design of multi-centre validation studies and to consider whether data generated in the latter might also be used for product-specific validation purposes. The second part of the workshop focused on aspects of validation within the consistency approach context.

The minutes of the workshop summarising the presentations, discussions, recommendations and conclusions formed the basis for the workshop report *Recommendations of the VAC2VAC workshop on the design of multi-centre validation studies*.

VAC2VAC principles were presented and discussed with the Belgian, Austrian, Finish and Dutch national regulatory authorities.

Outreach and Communication

The VAC2VAC project was presented at the following meetings:

Arnoud Akkermans (RIVM) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at the European Directorate for the Quality of Medicines (EDQM) expert group 15 meeting, 28-29 March 2017.

Marcel Hoefnagel (MEB) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at the CASSS Bio-assays meeting, 8-9 May 2017, Washington, USA.

Heidemarie Schindl (AGES) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at the annual Official Medicines Control Laboratory (OMCL) meeting, 17 May 2017, Budapest, Hungary.

Catrina Stirling (Zoetis) presented VAC2VAC as part of the presentation "3Rs in the EU where are we" at the USDA/AHI on 15 June 2017.

Marlies Halder (JRC) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at the J3RsWG (The Joint Committee for Medicinal Products for Veterinary Use/Committee for Medicinal Products for Human Use Working Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products) meeting on 20 June 2017.

Larry Bondoc (Boehringer Ingelheim) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at 2 seminars at 2 different departments at the University of the Philippines at Los Baños, Philippines on 30 June 2017.

Joris Vandeputte (IABS-EU) presented VAC2VAC as part of the presentation "Development to preparedness for Threats and Globalization in the next decades" at 8th Thai National Vaccine Conference, on 19 July 2017, Bangkok, Thailand.

Cyrille Krul (HU) presented the poster "A kinomics approach to safety testing: towards an animal free safety test for whooping cough vaccines" at the 10th Congress on Alternatives and Animal Use in the Life Sciences on 20-24 August 2017 in Seattle, USA.

Coenraad Hendriksen (Intravacc) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at the 10th Congress on Alternatives and Animal Use in the Life Sciences on 20-24 August 2017 in Seattle, USA.

Jeffrey Bajramovic (BPRC) presented the poster "Profiling of innate immune responses to determine vaccine quality as part of the consistency approach" at the 10th Congress on Alternatives and Animal Use in the Life Sciences on 20-24 August 2017 in Seattle, US.

Dieter Pullirsch (AGES) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at the 10th Annual EUR Bioassay Conference, St. Julians, Malta.

Hilde Depraetere (EVI) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at the International Society for Vaccines (ISV) Annual Congress 5-7 October 2017, Paris, France.

Karl-Heinz Bucheit (VAC2VAC SAC, EDQM) presented "VAC2VAC progress year 1" at the WHO Expert Committee on Biological Standardization (ECBS) meeting 10-12 October 2017.

Coenraad Hendriksen (Intravacc) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at Animal Cell Technology Industrial Platform meeting, 30 November – 1 December 2017, Nantes, France.

Carlos Vega (Boehringer-Ingelheim) presented "Vaccine batch to vaccine batch comparison by consistency testing (VAC2VAC)" at the CONASA meeting, 4-8 December 2017, Mexico.

Joris Vandeputte (IABS-EU) presented VAC2VAC to the Finnish and Austrian regulatory agencies on 27 November and 13 December 2017, respectively.

STANDARDISATION AND DEVELOPMENT OF ASSAYS FOR

the assessment of influenza vaccine correlates of protection

FLUCOP

Despite the fact that influenza vaccines have been developed and licensed for many years, and despite the clinical evidence existing concerning their ability to protect against influenza, correlates of protection induced by these vaccines are still not fully understood.

To address this deficiency, FLUCOP aims to develop and make available a toolbox of standardised, validated serological assays for human influenza vaccines, agreed and used by key parties in the public and private sectors, tools which will have a tremendous impact on influenza vaccine R&D and will pave the way for future investigations and the further definition of correlates of protection for these vaccines.

The FLUCOP project is supported by IMI and EFPIA, which together provide a total funding of €14M (half of which is provided in cash by IMI, the other half in kind by EFPIA). The project commenced in March 2015 with a five year-duration. EVI in particular is in charge of dissemination and communication in FLUCOP.

The long-term objective of FLUCOP is to improve and standardise existing immunological assays for the definition of correlates of protection in future efficacy trials and to develop new assays to better evaluate influenza vaccine immunogenicity.

These overall objectives will be achieved through the following specific objectives:

- Standardisation of haemagglutination inhibition and virus neutralisation assays (primary objective).
- Advancing the understanding and application of cell-mediated immunity and NA assays as tools to evaluate the performance of influenza vaccines (secondary objective).
- Consideration of new technologies that could be used to investigate correlates of protection and population-based evaluations of influenza vaccines (exploratory objective).

RECENT ACHIEVEMENTS Further progress has been achieved in the development of assays to detect neuraminidase (NA)-specific antibody responses for evaluating influenza vaccines immunogenicity and in the development of new technologies that eventually could be applied to population based evaluations of influenza vaccines.

PARTNERS

- Abbott, The Netherlands
- Artemis One Health Research BV, The Netherlands
- AstraZeneca AB, Sweden
- Erasmus Universitair Medisch Centrum Rotterdam (EUMCR), The Netherlands
- European Medicines Agency (EMA), United Kingdom
- European Vaccine Initiative (EVI), Germany
- Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Italy
- Biomedical Primate Research Centre (BPRC), The Netherlands
- GlaxoSmithKline (GSK), Belgium
- Istituto Superiore di Sanità, Italy
- Janssen, The Netherlands
- MHRA-Department of Health,United Kingdom
- Novartis, Italy
- Paul-Ehrlich-Institut, Bundesinstitut Für Impfstoffe Und Biomedizinische Arzneimittel, Germany
- QUINTEN, France
- Sanofi Pasteur, France
- Sclavo Vaccines Association, Italy
- The Chancellor, Masters and Scholars of the University of Oxford, United Kingdom
- Università degli Studi di Siena, Italy
- Universiteit Gent, Belgium
- Universitetet i Bergen, Norway
- University of Surrey, United Kingdom

FLUCOP

Capacity strengthening, workshops, training

A second Assay Validation Workshop was held in Siena on 5 April 2017 which was attended by 36 participants from 22 FLUCOP institutions.

Harmonisation

Concerning the standardisation of HAI assays, pilot studies were initiated to test the standardised protocols developed. In the context of developing assays for CMI, the creation of a biobank with PBMCs initiated at project beginning was largely accomplished. The biobank ultimately to be used for the standardisation and evaluation of assays to measure influenza-specific cell-mediated immunity. PBMC have been collected pre- and post-vaccination, from blood samples from subjects vaccinated during two flu seasons, as well as from blood donors. In this context, protocols for isolation and freezing of PBMCs were standardised.

Outreach and Communication

News and updates concerning FLUCOP website were widely disseminated via the project's web page and by newsletters. Several scientific-technical findings and achievements from the project were published in leading peer-reviewed journals. The following presentations were made during 2017:

Hanna Sediri, PEI, presented "Development of an enzyme-linked-lectin-assay to measure influenza A virus neuraminidase specific antibodies" at the 27th Annual Meeting of German Society for Virology, Marburg, Germany, 22-25 March 2017.

Hanna Sediri, PEI, presented "Development of an enzyme-linked-lectin-assay to measure influenza A virus neuraminidase specific antibodies" at the Junior Scientist Zoonoses Meeting, Langen, Germany, 7-9 June 2017.

Patricia Londono-Hayes, Sanofi Pasteur and Donata Medaglini, University of Siena, presented "What have we learnt and how can we move forward?" at the Universal Influenza vaccines Workshop organised by the European Commission, Directorate General for Research & Innovation, Brussels, Belgium, 14 June 2017.

Patricia Londono-Hayes, Sanofi Pasteur, presented "Standardization and development of assays for assessment of influenza vaccines correlates of protection" at the18th World Vaccine Congress, Barcelona, Spain, 10-12 October 2017.

Members of the FLUCOP Steering Committee gave an update on progress presented to the Vaccines Working Party Meeting at the European Medicines Agency, London, UK, 17 November 2017.

EUROPEAN NETWORK OF VACCINE
Research and Development

TRANSVAC2

TRANSVAC2 is a collaboration-based infrastructure bringing together Europe's leading vaccine research institutes, including academic research institutes, public research institutions, SMEs, European infrastructures, Government institutions and product development partnerships (PDPs). Funding of €10.6M is provided by the European Union.

The main objective of TRANSVAC2 is to unite and strengthen existing European and national vaccine development programmes by forming a sustainable European vaccine research infrastructure capable of addressing European societal health-related challenges and strengthening Europe's competitive position. Institutions participating in TRANSVAC2 will address Europe's current vaccine-development challenges by:

1. Providing highly-demanded and badly needed scientific and technical services (TNA) to European vaccine developers.

2. Conducting joint research activities.

3. Implementing networking, communication, policy development, and federating activities.

TNA activities are tightly interlinked with innovative joint research activities (JRA) which, by improving the transnational services provided by TRANSVAC2, will directly strengthen, in an ongoing fashion, the value of the overall infrastructure. In line with the multi-disciplinary nature of vaccine development, these activities will be transdisciplinary and will focus in particular on the "translational gap" in vaccine R&D. TRANSVAC2's networking activities will strengthen cooperation among project participants, the scientific community, industry, and other key stakeholders such as funders, and policy and decision makers. TRANSVAC2 will contribute significantly to the European research area (ERA) by strengthening Europe's competitive position through the advancement of vaccine-related scientific and technological capabilities, and also addressing major EU scientific and societal challenges.

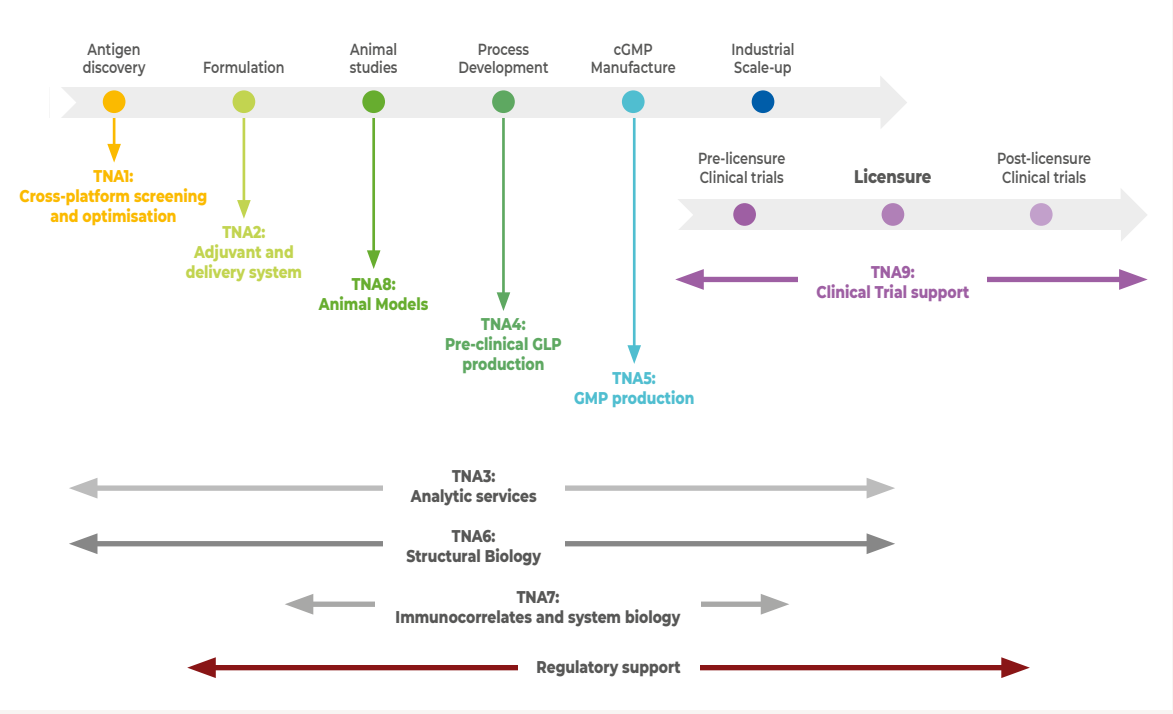
The project has started on 1st May 2017.

PARTNERS

- Bioaster, France
- Biomedical Primate Research Centre, The Netherlands
- Commissariat à l'Energie Atomique, France
- European Research Infrastructure for Translational Medicine (EATRIS), The Netherlands
- European Clinical Research Infrastructure Network, France
- European Vaccine Initiative, Germany
- Fraunhofer Institute for Molecular Biology and Applied Ecology, Germany
- GenIbet, Portugal
- Helmholtz Centre for Infection Research, Germany
- Institut de Recerca i Tecnologia Agroalimentàries, Spain
- Institut National de la Recherche Agronomique, France
- Institute for Translational Vaccinology, The Netherlands
- Instituto de Biologia Experimental e Tecnológica, Portugal
- Integrated Structural Biology Infrastructure for Europe, United Kingdom
- Leiden University Medical Centre, The Netherlands
- Leiden University, The Netherlands
- London School of Hygiene & Tropical Medicine, United Kingdom
- Public Health England and Medicines and Healthcare Products Regulatory Agency, United Kingdom
- Sclavo Vaccines Association, Italy
- Statens Serum Institut, Denmark
- Swiss Federal Institute of Technology in Zurich, Switzerland
- University of Lausanne, Switzerland
- University of Oxford, United Kingdom
- University of Siena, Italy
- Vaccine Formulation Institute, United Kingdom
- Wageningen Bioveterinary Research Institute, The Netherlands

Delivery Platform, Adjuvants and Viral Vectors

TRANSVAC2 will offer an integrated panel of services based on a "one-stop-shop" business model which will organise partner facilities into a single vaccine development pipeline, in which the different complementary units will work seamlessly and with a harmonised and efficient work-flow.



Platform "Technology"

This platform will focus on technologies for process development and GMP production. TRANSVAC2 will use a tiered system in which vaccine candidates will be tested using a diverse array of production systems including those based on bacterial, mammalian cells, and higher plant technologies. Both human and veterinary vaccines, for prophylactic and therapeutic applications, will be addressed by TRANSVAC2.

The service will provide centralised access to diverse production systems, analytical assays and process options, expertise in GMP manufacture, and the planning and execution of clinical trials according to good clinical practice (GCP).

Platform "Immunocorrelates and Systems Biology"

The Systems Biology Platform will offer a range of well-established services, and shall promote the development of next-generation systems biology technologies for the analysis of innate and adaptive immune responses to vaccination. Novel systems biology techniques will allow the integration of hierarchical levels of information, allowing the complexities of the interactions described above to be unravelled. Approaches will include "omics" technologies, including genomic, transcriptomic, proteomic and metabolomic analysis (complemented by computational biology to create databases), data pipelines, data visualisation tools, model building, and ultimately the capacity to simulate the necessary immune responses *in silico*.

Platform "Animal models"

Another critical step is assessing vaccine candidates using meaningful animal models. It is, however, a major challenge to ensure that data generated using animal models are relevant and informative for the development of human vaccines, as few scientifically-confirmed animal correlates-of-protection exist. The TRANSVAC2 Animal Platform will offer a comprehensive and unprecedented panel of animal models and associated innovative techniques, primarily for monitoring immune responses to vaccines and experimental infection. TRANSVAC2 will provide both valuable consultancy and act as a service provider for vaccine researchers' animal study needs.

Platform "Clinical Trials"

This platform will aim to prepare all vaccine candidates undergoing vaccine development within TRANSVAC2 so as to keep clinic-related issues under consideration at all times. Advanced consultancy will also be provided on a wide range of topics including trial design, methodologies, selection of sites, acquisition of funding, management, regulatory issues, and ethics.

Capacity strengthening, workshops, training

TRANSVAC2 training activities provide fundamental and advanced knowledge on a wide-range of vaccine development-related topics.

TRANSVAC2 offers training in the form of modules at leading European centres, creating customised international courses in vaccine R&D topics. In those modular and customised vaccinology training courses theoretical and practical training will be provided.

TRANSVAC2's aims to enhance the personal networks of the new generation of vaccine scientists through the project's training courses. The ultimate objective of the TRANSVAC2 consortium is to establish a sustainable pan-European training platform for vaccine development:

First calls for training courses will be launched in Q2 2018.

Harmonisation

TRANSVAC's joint research activities (JRAs) aim (i) to address current major gaps in vaccine development knowledge and are designed to feed directly into and to support the TNA activities (ii) to focus on improving predictive assays, adjuvants, animal models, and systems biology:

• develop assays that are of validated and reproducible benefit to vaccine development (Predictive assay research).

• develop stable formulations for rational improvement of the immune response (Adjuvants).

• improve the predictive value of animal models for vaccine evaluation, provide consultancy on the selection of appropriate models, and develop innovative approaches to characterise *in vivo* antigen behaviour and host responses whilst reducing animal use (Animal models).

• identify and validate mathematical models that can accurately predict interactions between immune system components in relation to vaccination, as well as develop state-of-the-art methods for the structural and functional analysis of vaccine candidates (Systems biology).

Outreach and Communication

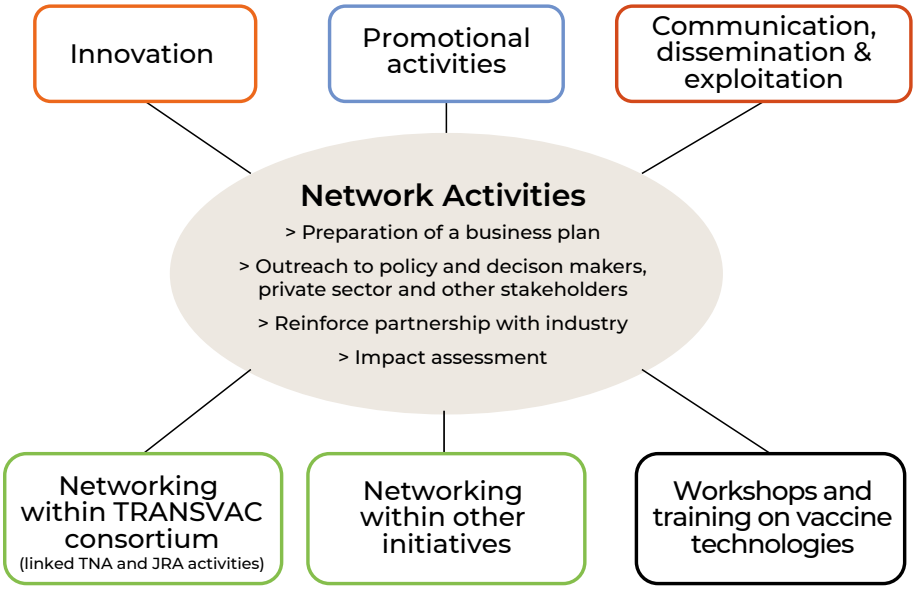
Stefan Jungbluth (EVI) presented TRANSVAC "European Vaccine Research and Development Infrastructure" at the Modern Vaccines Adjuvants & Delivery Systems (MVADS) conference, 12-14 September, Porto Portugal. At the same conference a flyer was distributed.

Maria Lawrenz (VFI) presented "Training in adjuvants and vaccine formulation" at the MVADS conference, 12-14 September, Porto Portugal.

Hilde Depraetere (EVI) presented a TRANSVAC poster at the International Society for Vaccines (ISV) Annual Congress, 5-7 October, Paris, France. At the same conference a flyer was distributed.

A TRANSVAC flyer was part of the conference pack at the Vaccines for Enteric Diseases meeting, 9-11 October, Albufeira, Portugal.

Nicola Viebig (EVI) presented a TRANSVAC poster at the ASTMH 66th Annual Meeting, 5-9 November, Baltimore, USA.



TRAINING

LIVE

"Leading International Vaccinology Education" (LIVE), is an Erasmus Mundus – Joint Master Degrees funded by the Education, Audiovisual and Culture Executive Agency (EACEA) of the European Commission, which started in 2016. EVI is an associated partner. Dr. Odile Leroy is a member of the Academic and Management Board.[65]

The general objective of the new LIVE programme is to train the next generation of vaccinologists who will have to manage an increasing number of infectious and non-infectious vaccine targets for many important issues: unsolved and still emerging infectious diseases, immune-senescence in an era where there is exponential aging of the population, non-infectious but immune-related diseases (e.g. allergy, cancer and chronic inflammatory diseases such as atherosclerosis, obesity, diabetes, addictions…).

Such needs parallel the global need to decrease health care expenditures while increasing quality and health care outcomes. Meeting these needs starts with providing the funding, teachers, excellent training and career pathways for smart and dedicated students who will devote their professional careers to Vaccinology. LIVE is a two-year programme for talented and motivated students interested in multidisciplinary studies in Vaccinology.

It is a joint project between five European universities (Barcelona, Antwerp, Saint-Etienne and Lyon), each one awarding a Master degree of excellent quality. Academic internationality is enriched by a worldwide network of 12 academic universities from Brazil, Canada, China, Cuba, Europe, and USA and 13 industrial partners and vaccine manufacturers. LIVE students will develop a trans-national appreciation for vaccine issues by in-residence participation in educational activities in at least three different countries during the programme.

Graduates are also well prepared for doctorate research in PhD programmes funded by associated partners. We anticipate that the LIVE programme, designed as an interdisciplinary teaching approach and an internationally composed student community, will provide students with these five fundamental keys to engage in successful careers in vaccinology, and to build an international network of professionals who will help to solve the current and future challenges of the field.

65. http://live.univ-lyon1.fr/webapp/website/website.html?id=3743907&pageId=275152 (accessed 29-05-2017)

EDCTP/TDR Fellowships - Training at EVI

The strengthening of public health and vaccine research capacities in Low- and Middle-Income Countries (LMICs) is part of EVI's mission to combat diseases of poverty. Therefore, EVI joined the EDCTP/TDR Clinical Research and Development Fellowship Scheme in 2016 as a hosting institution providing training to researchers from LMICs who are involved in clinical research projects.

The purpose of the EDCTP/TDR Joint Call for Clinical Research and Development Fellowships is to support researchers and key members of clinical trial research teams from low and middle-income countries (LMICs) to acquire specialist skills in clinical research and development through placements in pharmaceutical companies and PDPs. The scheme targets junior to mid-career researchers or clinical staff (clinicians, pharmacists, medical statisticians, data managers, other health researchers) who are employed by a legal entity in LMICs where they are currently working on activities in the scope of EDCTP or TDR. Fellows must be committed to return to their home organisation for a minimum of two years after completion of the fellowship to transfer the skills acquired to their home institution.

The training of scientists is key in the empowerment of research institutions in LIMCs, to address public health challenges and develop and implement appropriate solutions. The goal of the placement at EVI is to strengthen the fellow´s capabilities in clinical research implementation according to international guidelines particularly for early stage vaccines development. Following the spirit of EDCTP-TDR, the training at EVI aims

to facilitate critical decision-making in vaccinology by providing fellows with an overview of the field, from antigen discovery to vaccine development and clinical trials as well as the socio-economic, regulatory and ethical issues of vaccination.

The training methodology has two complementary approaches: a series of lectures combined with hands-on training. Topics covered include, among others, project management, preclinical and clinical development of vaccines, GMP manufacturing and regulatory aspects. Under the supervision of the EVI Executive Director, Odile Leroy, an experienced EVI staff member is allocated as a mentor to the trainee. The mentoring concept encourages the trainees to take personal responsibility of project tasks, offers assistance and stimulates individual creativity.

"We expect that after successful completion of this training programme, our fellows will contribute to promote high quality research in LMICs. One strategy for this is training of peers, as stated in the reintegration plan of the trainees, and the other is the strengthening of collaborative work and networking, which is facilitated by the network of EVI partners", says Odile Leroy.

In 2016, two researchers from Burkina Faso were hosted by EVI. In 2017, one researcher from Colombia and one researcher from Burkina Faso with different educational background and working experiences were awarded with the EDCTP/TDR fellowship and spent one year at EVI in Heidelberg, Germany supporting EVI staff and acquiring key competencies in vaccine development and project management. After their return to their home institution, EVI maintains a close interaction and continues to mentor the trainees. In October 2017, Nicola Viebig was invited by the former fellow Fabrice Somé to Burkina Faso to visit the institution and field sites and to provide training and advice to the young IRSS scientists.

Following the positive experience in 2016 and 2017, EVI is happy to welcome two new trainees in 2018.

Advocacy and International Fora

The year 2017 offered many opportunities at national, international and European levels to advocate for global health R&D. In addition to numerous direct interactions which took place with relevant stakeholders, EVI provided input and expertise to a series of policy consultations, surveys and questionnaires that were launched by different funders and policy/decision makers such as, for example, CEPI, EDCTP2 and the EC.

In addition to these advocacy efforts, EVI actively participated in a variety of events as part of the institutional advocacy strategy to support vaccine development for diseases of poverty.

ADVOCACY

International Conference on Poverty-Related and Neglected Diseases: from funding to reaching universal health coverage, 1 February, Brussels, Belgium

The conference was on the outcomes of a one year study aimed to assess the impact of EU-funded research on poverty-related and neglected diseases (PRNDs) and how it has contributed to achieving universal health coverage and improving the health situation in low- and middle-income countries (LMICs). The conference aimed to discuss and disseminate the PRND study findings and recommendations to key stakeholders and to ensure that the views of key stakeholders are reflected in the final study report. In addition, the conference discussed how to best link EU research and development policy to ensure a maximal impact. The conference was attended by Odile Leroy.

CEPI Scientific Conference, in collaboration with INSERM, 21-22 February, Paris, France

The meeting programme concentrated on CEPI's initial target diseases MERS, Nipah, Lassa as well as Ebola and Zika. Additional discussions focussed on how to prepare for clinical trials during emergencies and utilise platform technologies to improve epidemic response. The meeting was attended by Stefan Jungbluth and Odile Leroy.

HSV Vaccine Preferred Product Characteristics (PPCs), Global Stakeholder Consultation, 29-30 March, Geneva, Switzerland

To begin the process of developing WHO's PPCs for HSV vaccines, the Immunization, Vaccines and Biologicals Department (IVB), in collaboration with the Department of Reproductive Health and Research (RHR), convened a global stakeholder consultation to consider the public health needs for HSV vaccine and key considerations for HSV vaccine preferences, particularly in LMICs where the need for a vaccine may be greatest. The Global Stakeholder Consultation was attended by Odile Leroy.

Dutch PDP annual meeting 'Access to medicine and partnerships', 13 April, The Hague, The Netherlands

The Dutch Ministry of Foreign Affairs financially supported PDPs that contribute to innovation of healthcare products and technologies specifically aimed at diseases and conditions related to poverty and sexual and reproductive health and rights. This event offers an excellent opportunity to exchange ideas and interact with representatives from PDPs and the Dutch PDP partners. EVI was represented by Nicola Viebig.

2017 WHO Product Development for Vaccines Advisory Committee (PDVAC) Consultation, 21-23 June, Geneva, Switzerland

PDVAC's remit is focused on vaccines that have a particular application to low and middle income countries (LMICs), and to facilitate product development in an effort to accelerate vaccine availability and access in these contexts. This 4th PDVAC meeting reviewed advances in pathogens where PDVAC has been engaging since 2014, as well as to review how PDVAC is collaborating with other vaccine development efforts across WHO. Several cross-cutting aspects that facilitate acceleration of development of vaccines for LMICs were also discussed. This meeting was attended by Odile Leroy.

EU advocacy on Global Health R&D: Strategy Workshop, DSW, 21 September, Brussels, Belgium

A meeting of product development partnerships, NGOs and other global health stakeholders took place in Brussels in order to exchange information about latest policy developments in the field and to discuss ways to align and coordinate future advocacy activities on European level. Stefan Jungbluth participated in this event.

World Health Summit 2017, 15-17 October, Berlin, Germany

The World Health Summit is the annual conference of the M8 Alliance of Academic Health Centers, Universities and National Academies. It aims to improve health all over the planet, catalysing that process through collaboration and open dialogue, and steering tomorrow's agenda to improve research, education, healthcare, and policy outcomes. It brings together researchers, physicians, key government officials, and representatives from industry as well as from NGOs and healthcare systems all over the world to address the most pressing issues facing every facet of healthcare and medicine in the upcoming decade and beyond. EVI was represented by Siaka Débé and Odile Leroy.

BioRN Annual Conference 2017, 24 October, Mannheim, Germany

The conference with the title "Revolution through Convolution – combining medtech, biotech and digital health to promote health science in our region" attracted about 120 participants from the BioRN Cluster and from the national and international life-science industry, among them representatives of the "Health Axis Europe" from Leuven and Maastricht. The conference accentuated the importance of the liaison of different technologies and strong collaborations to drive future innovation. The conference was attended by Hilde Depraetere and Nicola Viebig.

The European Vaccine Initiative–Accelerating vaccine development for diseases of poverty

Presentation by Stefan Jungbluth at the Instituto de Salud Carlos III, 6 November, Madrid, Spain.

INTERNATIONAL FORA ATTENDED

Influenza Vaccines for the World (IVW) 2017, 19–21 April, Lausanne, Switzerland

The sixth international conference and exhibition of this important series of influenza vaccine meetings was held in 2017. The IVW conference series focuses on 'Influenza Vaccination Issues'. It is an international forum for world renowned experts in the field of influenza vaccines and related issues (adjuvants/delivery/vaccination strategies) to report on the latest data and trends associated with current and new influenza vaccines/technologies and their availability/delivery/implementation worldwide. EVI was represented by Flavia D'Alessio and Sophie Houard.

WorldLeish-6 Congress, 16–20 May, Toledo, Spain

This two-yearly congress addressed issues ranging from molecules to disease control, with the patient as the main focus. The agenda included contemporary lectures, hot-topic sessions and satellite symposia covering the latest developments related to leishmaniasis. The programme was complemented by an educational programme covering basic research and clinical issues. EVI was represented at this meeting by María del Mar Castro and Stefan Jungbluth.

Zika virus and other mosquito-borne viruses. Science for preparedness and response in the Mediterranean region, 23–24 May, Barcelona, Spain

The event aimed to generate a forum for an interdisciplinary and international debate bringing together experts from different backgrounds to discuss about the critical issues related to public health, epidemiology, entomology, virology, clinical care and diagnostics. EVI was represented by Odile Leroy who presented "Zika virus and other mosquito-borne viruses".

100 Jahre Tropenmedizin an der Universität Tübingen, 29 June – 2 July, Tübingen, Germany

The first professorship for Tropical Medicine at the Medical Faculty of the University of Tübingen was established on the 2 July 1917. The University celebrated the 100 years of tropical medicine with a program including concerts, exhibitions, public readings and a symposium. The symposium was attended by Nicola Viebig.

Modern vaccines adjuvants & delivery systems, 12–14 September, Porto, Portugal

In light of the need for new and improved adjuvantation/delivery systems, this international conference provided an update on new adjuvant/delivery systems/technologies associated with developing modern vaccines strategies and vaccine research and offered its participants a forum to discuss issues in detail. Stefan Jungbluth gave an overview of the TRANSVAC2 vaccine R&D infrastructure in an oral presentation.

Symposium "New Horizons for measles-based vaccines and therapies - making and regulating", 13–14 September, Vienna, Austria

The symposium organised by Themis Bioscience brought together a selected group of experts from academia and industry, to discuss opportunities, challenges and recent progresses on measles-based vector systems. Odile Leroy was invited as a panellist.

18th Developing Countries Vaccine Manufacturers Network (DCVMN) annual general meeting, 25–28 September, Seoul, South Korea

The DCVMN is a public health driven, international alliance of manufacturers, working to strengthen vaccine manufacturers through the provision of information and professional training programs, technology improvements, innovative vaccine research and development, encouraging technology transfer initiatives, and educating the public about the availability of safe, effective and affordable vaccines for all people. EVI was represented at the annual general meeting by Odile Leroy who was invited to present the ZIKAVAX activities.

International Society for Vaccines (ISV) Annual Congress, 5–7 October 2017, Paris, France

The ISV Annual Congress is the world's largest scientific conference in the field of vaccines and covers a broad range of topics related to vaccines and immunotherapies. It will bring together individuals from all sectors of the global vaccine community to hear about the latest advances in the field, discuss challenges and opportunities, and network. EVI was represented by Odile Leroy and Hilde Depraetere.

ETEC and Shigella Vaccine Preferred Product Characteristics (PPCs), Global Stakeholder Consultation, 6-7 October, Albufeira, Portugal

The meeting, organised by WHO's Department of Immunization, Vaccines and Biologicals, had the goal to define the priority public health needs that should be addressed by ETEC and Shigella vaccines from a LMIC perspective. Moreover, it aimed at outlining key considerations for ETEC and Shigella vaccine preferences in the context of the pathogen epidemiology, natural history, and vaccine technical feasibility and considered the feasibility and potential impact of ETEC and Shigella vaccine approaches currently in development in light of the established public health needs. Stefan Jungbluth attended the meeting.

Vaccines for enteric diseases, 9-11 October, Albufeira, Portugal

The conference addressed diverse aspects of vaccines to counter human enteric diseases and provided a platform for researchers to present the current state of development of their particular vaccine candidates. Given the difficulties faced in improving the sanitary conditions in large areas of the developing world and the increasing resistance to bacterial enteric pathogens to antibiotics, the meeting highlighted the importance of enteric vaccines as tools for disease prevention. Stefan Jungbluth participated in this conference.

10th European Congress on Tropical Medicine and International Health, 16-20 October, Antwerp, Belgium

The meeting provided a platform for state-of-the-art updates and recent breakthroughs in the field of tropical medicine and global health. It was a forum for reflection on the role and position of tropical medicine, global health and international cooperation in the 21st century, taking into consideration disruptive changes such as human migration, environmental evolution, technological innovation and political power shifts. The meeting was attended by María del Mar Castro.

American Society of Tropical Medicine and Hygiene (ASTMH) 66th Annual Meeting, 5-9 November, Baltimore, USA

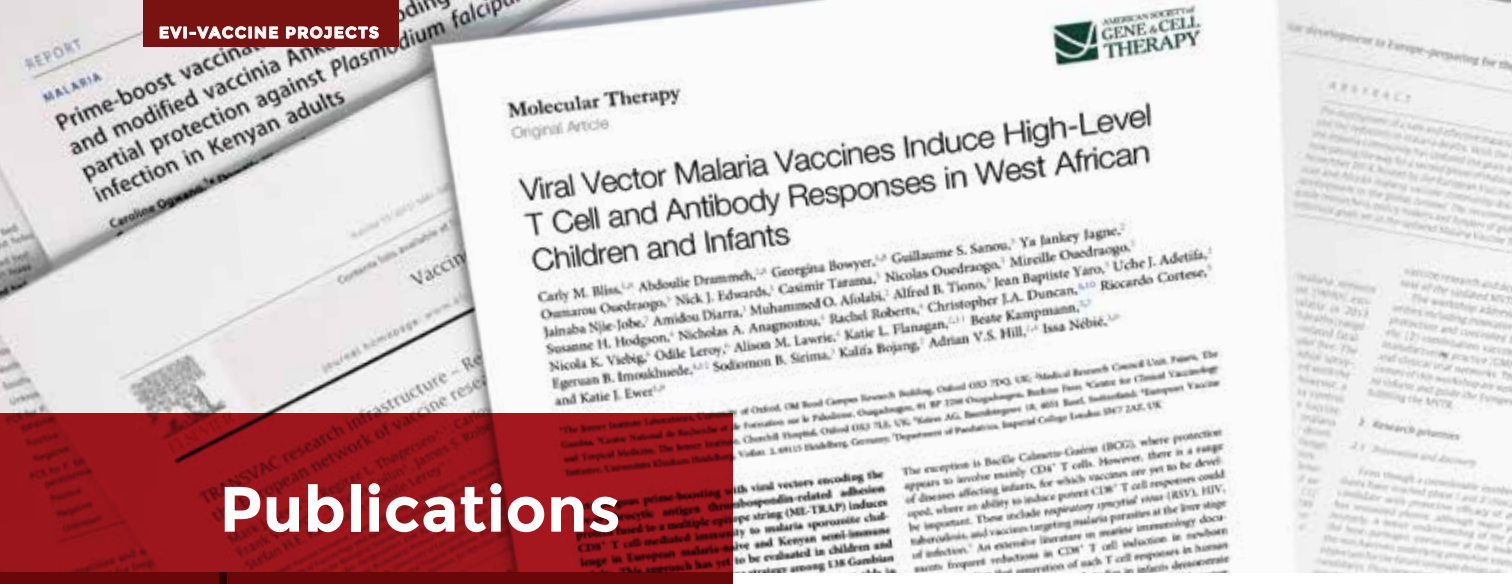
The ASTMH Annual Meeting draws tropical medicine and global health professionals representing academia, government, non-profits, philanthropy, NGOs, industry, military and private practice. The meeting is designed for researchers, professors, government and public health officials, military personnel, travel clinic physicians, practicing physicians in tropical medicine, students and all health care providers working in the fields of tropical medicine, hygiene and global health. The Annual Meeting is a five-day educational conference that includes four pre-meeting courses and draws approximately 4,600 attendees. EVI was represented by Nicola Viebig.

III International conference on VACCINES RESEARCH AND DEVELOPMENT (Vaccine R&D conference), 13-15 November, Washington, USA

The Vaccines R&D conference brought together experts of the leading scientists and professionals institutes to share not only their knowledge, but their findings in the development of vaccine research. This conference was attended by Odile Leroy.

GHIT R&D Forum, 8 December, Tokyo, Japan

The forum offered the opportunity for GHIT's product development partners to present the latest progress achieved and facilitated the exchange of ideas and experience among diverse organisations and scientists that attended the meeting. Stefan Jungbluth represented EVI on this occasion.



Publications

MALARIA VACCINES

AMA1-DiCo

Sirima SB, Durier C, Kara L, Houard S, Gansane A, Loulergue P, Bahuaud M, Benhamouda N, Nebié I, Faber B, Remarque E, Launay O; AMA1-DiCo Study Group. Safety and immunogenicity of a recombinant *Plasmodium falciparum* AMA1-DiCo malaria vaccine adjuvanted with GLA-SE or Alhydrogel® in European and African adults: A phase 1a/1b, randomized, double-blind multi-centre trial. Vaccine. 2017 Oct 27;35(45):6218-6227. doi: 10.1016/j.vaccine.2017.09.027.

MultiMalVax

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MVVC

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MVVC 2

Mensah VA, Roetynck S, Kanteh EK, Bowyer G, Ndaw A, Oko F, Bliss CM, Jagne YJ, Cortese R, Nicosia A, Roberts R, D'Alessio F, Leroy O, Faye B, Kampmann B, Cisse B, Bojang K, Gerry S, Viebig NK, Lawrie AM, Clarke E, Imoukhuede EB, Ewer KJ, Hill AVS, Afolabi MO. Safety and Immunogenicity of Malaria Vectored Vaccines Given with Routine Expanded Program on Immunization Vaccines in Gambian Infants and Neonates: A Randomized Controlled Trial. Front Immunol. 2017 Nov 20;8:1551. doi: 10.3389/fimmu.2017.01551. eCollection 2017. PMID: 29213269.

PlacMalVac

Gbédandé K, Fievet N, Viwami F, Ezinmegnon S, Issifou S, Chippaux JP, Dossou Y, Moutairou K,

Massougbodji A, Ndam N, de Jongh WA, Søgaard TMM, Salanti A, Nielsen MA, Esen M, Mordmüller B, Deloron P, Luty AJF; Multi-centre research paper. Clinical development of a VAR2CSA-based placental malaria vaccine PAMVAC: Quantifying vaccine antigen-specific memory B & T cell activity in Beninese primigravidae. Vaccine. 2017 Jun 14;35(27):3474-3481. doi: 10.1016/j.vaccine.2017.05.027.

Pehrson C, Salanti A, Theander TG, Nielsen MA. Pre-clinical and clinical development of the first placental malaria vaccine. Expert Rev Vaccines. 2017 Jun;16(6):613-624. doi: 10.1080/14760584.2017.1322512.

Pehrson C, Heno KK, Adams Y, Resende M, Mathiesen L, Soegaard M, de Jongh WA, Theander TG, Salanti A, Nielsen MA. Comparison of functional assays used in the clinical development of a placental malaria vaccine. Vaccine. 2017 Jan 23;35(4):610-618. doi: 10.1016/j.vaccine.2016.12.028.

VIRAL VACCINES

EDUFLUVAC

Carvalho SB, Fortuna AR, Wolff M, Peixoto C, Alves PM, Reichl U, Carrondo MJT (2017b) Purification of influenza virus-like particles using sulfated cellulose membrane adsorbers. J Chem Technol Biotechnol. Accepted Author Manuscript. DOI:10.1002/jctb.5474.

Carvalho SB, Moleirinho MG, Wheatley D, Welsh J, Gantier R, Alves PM, Peixoto C, Carrondo MJT (2017a) Universal label-free in-process quantification of influenza virus-like particles. Biotechnol J, 12: n/a, 1700031. DOI:10.1002/biot.201700031.

Pavlova S, D'Alessio F, Houard S, Remarque EJ, Stockhofe N, Engelhardt OG. Workshop report: Immunoassay standardisation for "universal" influenza vaccines. Influenza and other Respiratory Viruses. 2017. DOI: 10.1111/irv.12445.

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De Vries RD, Nieuwkoop NJ, Pronk M, de Bruin E, Leroux-Roels G, Huijskens EGW, van Binnendijk RS, Krammer F, Koopmans MPG, Rimmelzwaan GF. Influenza virus-specific antibody dependent cellular cytoxicity induced by vaccination or natural infection. Vaccine. 2017 Jan 5;35(2):238-247. doi: 10.1016/j.vaccine.2016.11.082. Epub 2016 Nov 30.

De Vries RD, Nieuwkoop NJ, van der Klis FRM, Koopmans MPG1, Krammer F, Rimmelzwaan GF. Primary Human Influenza B Virus Infection Induces Cross-Lineage Hemagglutinin Stalk-Specific Antibodies Mediating Antibody-Dependent cellular Cytoxicity. J Infect Dis. 2017 Dec 27;217(1):3-11. doi: 10.1093/infdis/jix546.

Financial performance report

EVI receives funding from national and international governmental agencies, as well as private organisations. EVI uses those funds to finance a broad portfolio of projects, which help to accelerate the development and clinical assessment of vaccine candidates for diseases of poverty, to promote the affordability and accessibility of those vaccines, and to act as a focal point to enhance the alignment of all major stakeholders in the area of vaccine development for diseases of poverty. The strategic objective is to improve the worldwide access of people in need of adequate and affordable vaccines. In the course of 2017, EVI made major impact fundraising efforts with two new major clinical development projects starting in early 2018 and with the aim of more to come. EVI will thus be a leading partner in various clinical trials and is facing a promising progression for years to come.

PORTFOLIO FUNDING

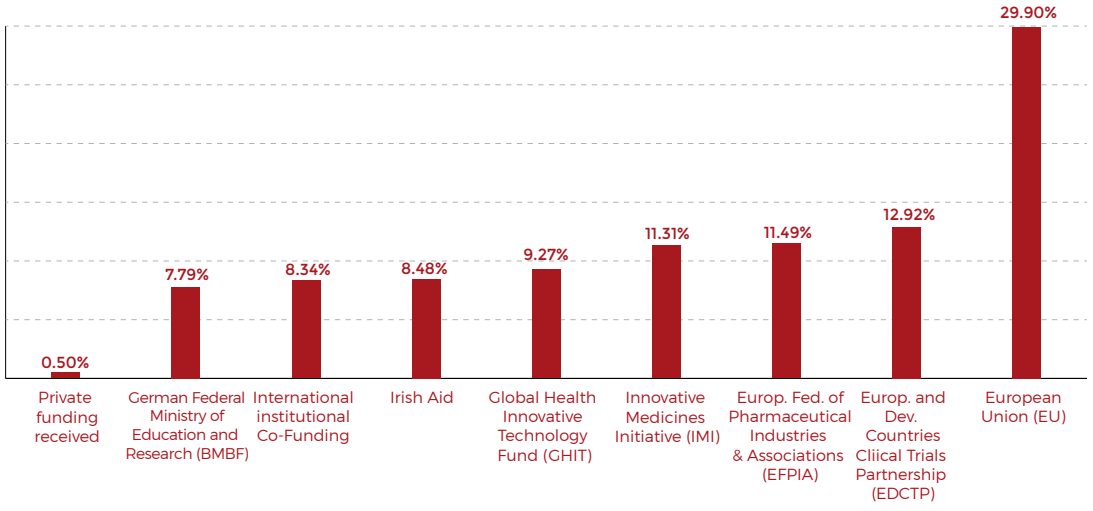
EVI's project portfolio as of 31 December 2017 comprises eight active projects in the broad field of translational vaccine R&D, transnational access services and capacity building, and of course vaccine development in general through clinical trials. Six projects were contractually concluded in 2017, two new projects could be secured wich will start beginning of 2018. EVI succeeded in raising significant funds of several million Euros. Most of this funding will be applicable to projects in 2018 and beyond. At the same time, fundraising efforts are expected to yield new projects and funding schemes during 2018. Same as in the last years, EVI appreciates the establishment of new partnerships and valuates highly the continued support by its long-term partners.

Since its establishment in Heidelberg, Germany, in 2009, EVI has raised in total more than €122 million together with its partners, which have been used to fund primarily its projects, scientific partners and lastly to sustain its secretariat. In fact more than 86% or €106 million of all fundraising has gone uncut to GMP production, clinical development and direct support for the scientist institutions. On top of this comes the work of EVI staff on the projects which thereafter leaves an only small percentage of costs for general management. Furthermore, EVI has successfully diversified its funding sources in order to reduce its financial risks and continues through R&D innovations to target new business opportunities globally.

EVI has likewise managed to diversify its collaborations and fundraising efforts with partner organisations from all over the world. In 2018 EVI will once again expand its operations in Africa, now including new nations such as Sudan and Ethiopia on top of all the other nations EVI cooperates with and is working every day to include new partners and nations in the quest to combat diseases of poverty.

Diseases know no boundaries, and although the diseases, that the work of EVI is involved with, are linked to poverty, the EVI mission is not restricted to offering poverty-stricken populations a safer life, stronger opportunities and economies of scale and scope. Indeed, the impact of global migration and global warming brings an unprecedented challenge to combat diseases of poverty before they spread and affect even more people. In addition to its work in the field of vaccine development, EVI recognises the importance to combat climate changes, as this has a profound negative impact on the spread of terrible diseases previously confined to geographic areas but now in the risk of spreading.

FIGURE 2 DISTRIBUTION OF FUNDS RECEIVED BY OR PLEDGED TO EVI AS COORDINATOR SINCE 2009 (AS OF 31/12/2017) IN %



FINANCIAL EFFICIENCY

Between 2009 and 2017 every single euro of invested EVI funds has leveraged through matched co-funding and in-kind contributions approximately €5.50 of R&D value.

For EVI the key factor is synergy in all actions and processes to optimize the output. The donors to EVI have every right to expect an added value to their investments and EVI makes every effort to meet their expectations, which historically proven are delivered. Yet one substantial challenge, that EVI is facing, are the high expectations for good governance and high-quality administration against the lack of funding opportunities for the same. Advocacy is therefore paramount to explain the strong linkage between good governance and high-quality administration on the one side and the efficient and successful project implementation connected to it, as it has been done by EVI in the last 20 years and for which EVI aims to continue for many more years to come.

Concerning the deployment of funds and activities in 2017, EVI has continued to focus on streamlining and improving its processes to maximise the usage of funds in its portfolio of projects and to minimise administrative expenses by expanding the usage of our enterprise resource planning (ERP) software – SAP Business ByDesign. Implementation of SAP has led to further significant

FIGURE 3 REALISED AND FORECASTED EVI INCOME AND EXPENSES

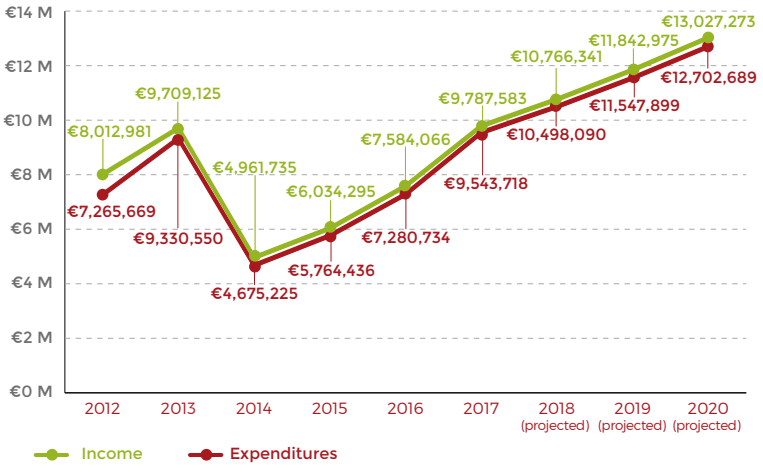


TABLE 2 DEVELOPMENT OF MANAGEMENT COSTS (IN % OF TOTAL COSTS)

Management percentage (excluding core initiative costs)			
Year	Upper threshold	Result	Direct investment percentage of each euro donated
2013	7%	3.7%	96.3%
2014	7%	7.0%	93.0%
2015	7%	0.6%	99.4%
2016	7%	6.27%	93.73%
2017	7%	1.33%	98.77%

improvements in terms of information availability and quality to enhance further the work and controls within the projects.

With the aim to minimise management costs while maintaining or improving quality, through reviewing and optimising the administrative processes EVI has succeeded in keeping the share of management costs low. It is the opinion of EVI, that donations and funding in general should be used for the vision and mission of EVI, and other cost factors should be minimised, which do not generate an added value for the true beneficiaries – the people. Therefore, EVI is always striving for a maximum utilisation of funds for the benefit of vaccine development and the children and adults urgently in need of vaccines against poverty related diseases. This strategy has led EVI for the sixth consecutive year to limit its management costs to below 7% of total costs per calendar year. Consequently, a minimum of 93% of funds could be invested into the projects. Facing increased global controlling and reporting requirements, EVI envisages that administration costs may rise beyond this threshold in the future.

The management percentage represents a share of the total incurred costs, which are only indirectly contributing to the progress of the science or the projects. It includes costs such as rent, utility, payroll management, general secretariat work, audit costs, tax management etc., which are essential for the work of the EVI secretariat and as such for the administration of the projects. No organisation can exist without these costs and they build the foundation for the projects to exist on. The percentage is calculated as the share of executive management costs in relation to the total costs of the organisation. Other costs earmarked to improve EVI's capacities in project management are consolidated as core initiative costs, which include EVI staff training, external communication and advocacy, as well as the cost coverage of EVI's governing and scientific advisory bodies. These costs represent the effort in creating new consortia across the world, the creation of new innovative projects with our partners that forms innovative science as defined in our name being an "initiative". The core initiative costs were equal to 5.6% of the total costs.

This results after subtraction of management and core initiative costs in a net investment of 93.07% of EVI's total funds directly on project development.

PORTFOLIO MANAGEMENT

EVI's activities over the current reporting period, during which expenditures were covering the broad portfolio of EVI, IMI, GHIT and EU projects, have produced major achievements at the given level of funding. The major part of activities in 2017 consisted of the conduct of clinical trials for the projects SEmalvac and LEISHDNAVAX as well as major developments of the free scientific services for European applicants provided through the TRANSVAC2 project. EVI concluded with the EDUFLUVAC project a 4-year project on the development of a universal flu vaccine, work that EVI aims to continue in the future. Lastly, the innovative state-of-the-art project VAC2VAC continued its work on replacing animal models in pre-clinical development where possible.

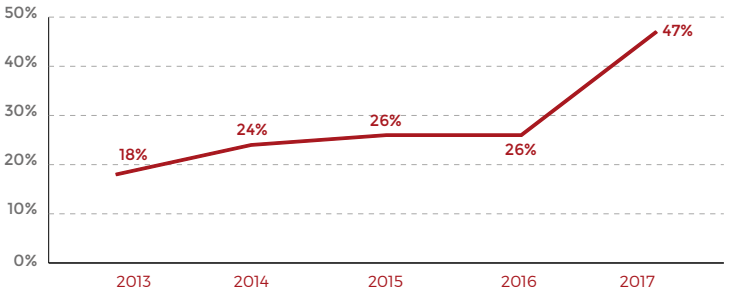
As a conclusion the current reporting period has shown, that the performance of EVI has been continuously efficient in its endeavours to accelerate the global development of vaccines against diseases of poverty.

KEY RATIOS

Regarding the EVI's capital structure, prudent financial budget, income and cost management has enabled EVI to continuously improve its equity base as another safety buffer for the sustainable financing of its operations. The EVI's enhanced equity base is reflected in the recent continuous increase of its equity ratio.[66]

EVI's current EU financial viability status in terms of key ratios is "good", which is the highest achievable grade in terms of sustainability, solvency, liquidity and profitability according to EU standards. EVI is supported by major organisations in Europe and is a financially strong organisation that appropriately incorporates possible risks and liabilities in its financial planning. EVI demonstrates a high level of responsibility toward its donors and stakeholders as shown by the strong ongoing ratios and equity forecasting. EVI understands the requirements of both the public and private investors, which focus on sound financial management and fiscal awareness. Thus, year by year,

FIGURE 4 EVI EQUITY RATIO 2012-2017



EVI takes its responsibility to the highest level of financial management.

Liquidity management is required to maintain a safe liquidity position and to ensure, after taking all applicable risks into consideration, the ability to fulfil current liabilities and obligations.

In 2017, EVI retained sufficient liquid funds and also met the required qualifications by donors and other public and private parties with an interest in EVI and its important work. This is reflected by the EVI's liquidity measurement ratios in 2017.

TABLE 3 EVI LIQUIDITY RATIOS 2017

Cash ratio (Cash + Cash equivalents)/Current liabilities)	1.54
Quick ratio (Cash + Cash equivalents + Accounts receivables)/Current liabilities)	1.71
Current ratio (Current assets/Current liabilities)	1.71

66. Equity Ratio = Total Equity Capital / Total Capital.

TRANSPARENCY

For the sake of transparency and donor requirements, EVI informs herewith about the number of staff according to payroll bracket, to which they refer to, in accordance with the stipulations of the German data protection act.

Payroll Level (in K€/year)	Number of staff including in house consultant
< 60	3
70-100	4
> 100	4

All information with regards to grants received by EVI in 2017, can be found in the following IFRS statement, as shown in note 6, including amongst others the attribution of grants to programmes and specific projects, payments, cost and revenues, as well as deferred income and expenses in 2017.

The accounting methodologies, IT system set-up and controls, as well as internal control measures in connection with financial and accounting principles of EVI ensure, that activities are adequately accounted for and attributed to the relevant projects or EVI tasks, eliminate the possibilities of duplications of transaction accountings and are regularly reviewed by certified external auditors.

EVI confirms that all tax affairs are in compliance with requirements of the jurisdiction of where EVI or its staff members have been tax registered in 2017, namely Germany, Denmark and Belgium.

For reason of transparency in relation to German GAAP and for easy comparability with German businesses and other national interest EVI present, its cash flow statement below as according to German GAAP.

The negative change of cash position despite a positive profit and loss result in 2017 is due to settlements of major payables from 2016 to clinical sites and project beneficiaries of EVI. As explained in the initial presentation 86% of all funds from fundraising over the years from 2009 are used uncut on GMP productions, clinical development and funding for scientist institutions, which can cause major changes in liquid funds from year to year as shown above and in the IFRS statement. However for other commercial entities this might be interpreted negatively but in the case of EVI it signifies the funding of projects and vaccine development as an expression of scientific progress.

TABLE 4 EVI GERMAN GAAP CASH FLOW 2017

	2017	2016
Net Income (result from ordinary operations)	**243,864.57**	305,043.50
Fixed Asset Depreciation and Retirement	**9,575.00**	18,127.03
Increase/(Decrease) of accruals	**(1,223,526.53)**	1,088,569.52
Increase/(Decrease) in accounts receivable (net)	**(827,253.79)**	(4,696.47)
Increase/(Decrease) in other receivable (net)	**17,427.97**	3,312.36
Increase/(Decrease) in accounts payable	**(826,178.20)**	(228,485.26)
Increase/(Decrease) in other payables	**361,136.10**	33,558.62
CF from operating activities	**(2,732,661.30)**	1,215,429.30
Fixed Asset Investments	**0.00**	(17,271.33)
CF from Investment activities	**0.00**	(17,271.33)
CF from financing activities	**3.00**	0.00
Change of Liquid funds	**(2,732,658.30)**	1,198,157.97

MANAGEMENT AND AUDITING

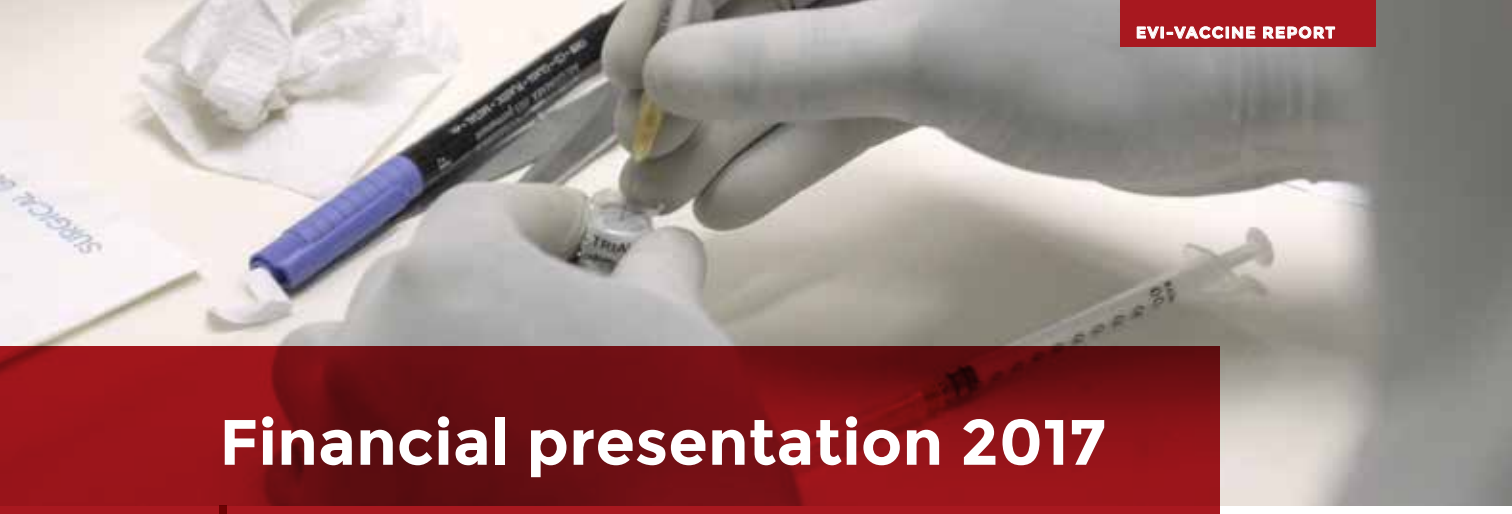
EVI has taken further measures to reduce risks caused by changes in its business environment, legal changes, currency risks, volatile financial markets and uncertainties regarding new funding sources. In addition to the obligatory annual project and company audits conducted by Falk & Co (Germany), these include annual voluntary financial audits of EVI's internal processes, risks and potential contingency measures by the external auditing company Prentis & Co. LLP (UK). The outcome of the audits is under review by EVI and is incorporated annually into EVI's processes and policies in order to optimise its protection against adverse effects. EVI also maintains relationships with major banks in Germany, UK and Denmark in order to perform global banking transactions at minimum costs, to move investments of temporary surplus funds into non-risk bearing assets and to diversify banking risks. The current negative interest rate at the European Central Bank has not affected EVI in terms of potential losses. In accordance with its accounting and reporting obligations, EVI's 2017 financial statements were prepared in compliance with German general accepted accounting principles (GAAP). In order to enhance the comparability of its financial statements with other international entities, EVI has also provided its financial statements according to international accounting standards/ international financial reporting standards (IAS/IFRS) on a voluntary basis since 2013. The following financial tables are extracted from the EVI statements according to IAS/IFRS.

We formally sign and approve the EVI annual financial report for the year ending 31 December 2017 in accordance with the EVI-EEIG Board decision.

We confirm that grants given to EVI were used in accordance with the terms and conditions provided for by each individual agreement.

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: 22/05/2018	Date: 22/05/2018	Date: 22/05/2018
Sten Larsen Finnsson, EVI Finance & HR Director	**Odile Leroy,** EVI Executive Director	**Clemens Kocken,** Chair of EVI-EEIG



Financial presentation 2017

TABLE 5 STATEMENT OF FINANCIAL POSITION AS OF 31 DECEMBER 2017

In EUR	Notes	2017	2016
CURRENT ASSETS			
Cash and cash equivalents			
Cash and banks - key accounts		2,992,427.83	4,257,086.13
Time deposits		1,782,000.00	3,250,000.00
Total cash and cash equivalents		**4,774,427.83**	**7,507,086.13**
Current accounts and receivables			
Trade receivables		1,042	0
Other receivables		539,664.85	24,496.32
Prepaid expenses		6,245.25	14,392.37
Total current accounts and receivables		**546,952.10**	**38,888.69**
Total current assets		**5,321,379.93**	**7,545,974.82**
Non-current assets			
Tangible fixed assets, net	**2**	15,404.00	24,979.00
Total non-current assets		**15,404.00**	**24,979.00**
Total assets		**5,336,783.93**	**7,570,953.82**
CURRENT LIABILITIES			
Liability to banks		11.36	0.00
Creditors	**3**	208,804.23	1,089,523.04
Accrued expenses	**4**	755,406.25	1,978,932.78
Other liabilities	**5**	29,530.85	92,181.45
Deferred income	**6**	2,111,866.72	2,423,016.60
Total current liabilities		**3,105,619.41**	**5,583,653.87**
Equity of organisation			
Operating result		243,864.57	305,043.50
Unrestricted operating funds		1,987,299.95	1,682,256.45
Total equity of the organisation		**2,231,164.52**	**1,987,299.95**
Total equity and liabilities		**5,336,783.93**	**7,570,953.82**

TABLE 6 STATEMENT OF COMPREHENSIVE INCOME FOR THE YEAR AS OF 31 DECEMBER 2017

In EUR	Notes	2017	2016
INCOME	7		
Turnover from sales		500.00	13,067.97
Public institutional funding	7		
Governmental & public international organisations		3,865,682.22	2,688,438.49
EU & IMI grants		5,906,243.02	4,745,128.88
EDCTP		0.00	244,440.02
Total public institutional funding	7	**9,771,925.24**	**7,678,007.39**
Other income net		13,915.62	(103,329.63)
Total income		**9,786,340.86**	**7,587,745.73**
SOCIAL MISSION EXPENDITURE			
Research & vaccine development expenditure	8		
EVI vaccine development projects		3,246,732.63	1,425,634.07
EU-funded research and vaccine development projects		4,967,535.60	2,649,385.81
IMI funded research and vaccine development projects		937,168.59	2,004,850.78
EDCTP-funded research and vaccine development projects		0.00	244,440.02
Advocacy & communications expenses		55,657.56	109,936.59
Total social mission expenditure		**9,207,094.38**	**6,434,247.27**
Supportive social mission expenditure	8		
Training, quality assurance and project development		19,851.61	52,854.55
Fundraising		138,281.15	185,400.92
Governance		51,849.58	151,969.60
Total supportive social mission expenditure		**209,982.34**	**390,225.07**
Non-social mission expenditure	8		
General executive administration		126,641.59	458,847.09
Total non-social mission expenditure		**126,641.59**	**458,847.09**
Total expenditure		**9,543,718.31**	**7,283,319.43**
Operating surplus/(loss)		245,106.57	304,426.30
OTHER INCOME (EXPENSES)			
Financial income, net	7	1,242.02	617.20
Total other income (expenses), net		**1,242.02**	**617.20**
Net surplus for the year prior to allocations		243,864.57	305,043.50
Allocation/(release) to restricted operating funds in equity		0	305,043.50
Allocation/(release) to unrestricted operating funds in equity		243,864.57	0.00
Net surplus for the year after allocations		**243,864.57**	**0.00**

TABLE 7 FUNDS FLOW STATEMENT FOR THE YEAR ENDED 31 DECEMBER 2017 (WITH 2016 COMPARATIVE FIGURES)

Funds flow from operations (In EUR)	2017	2016
Net surplus for the year	243,864.57	305,043.50
Depreciation of fixed assets	9,575.00	18,127.03
Increase (decrease) in provisions	(62,639.24)	67,338.81
(Increase) Decrease in other receivables	(516,210.53)	(4,696.47)
(Increase) Decrease in prepaid expenses	8,147.12	3,312.36
Increase (decrease) in creditors	(880,718.81)	(234,477.69)
Increase (decrease) in accrued expenses	(1,223,526.53)	1,088,569.52
Increase (decrease) in deferred income	(311,149.88)	(27,787.76)
Funds flow from operations	**(2,732,658.30)**	**1,215,429.30**

Funds flow from investing activities (In EUR)	2017	2016
(Increase) Decrease of investments in tangible fixed assets	(9,575.00)	(17,271.33)
Funds flow from investing activities	**(9,575.00)**	**(17,271.33)**

Funds flow from financing activities (In EUR)	2016	2015
Cash increase (decrease)	(2,732,658.30)	1,198,157.97
Cash and cash equivalents – beginning of year	7,507,086.13	6,308,928.16
Cash and cash equivalents – end of year	**4,774,427.83**	**7,507,086.13**

Statement of changes in equity for the year ended 31 December 2017 (EUR)	Opening balance	Allocation	Internal fund transfers	Closing balance
Internally generated funds as of 31 December 2016				
Paid-in capital	0.00	-	-	0.00
Surplus for the year	0.00	305,043.50	(305,043.50)	0.00
Restricted operating funds	0.00	-	0.00	0.00
Unrestricted operating funds	1,682,256.45	-	305,043.50	1,987,299.95
Capital of the organisation	**1,682,256.45**	**305,043.50**	**0.00**	**1,987,299.95**
Internally generated funds as of 31 December 2017				
Paid-in capital	0.00	-	-	0.00
Surplus for the year	0.00	243,864.57	(243,864.57)	0.00
Restricted operating funds	1,987,299.95	-	0.00	1,987,299.95
Unrestricted operating funds	0.00	-	243,864.57	243,864.57
Capital of the organisation	**1,987,299.95**	**243,864.57**	**0.00**	**2,231,164.52**

NOTES TO THE FINANCIAL STATEMENT FOR THE YEAR 2017

Note 1 - Significant Accounting Policies

(a) General comment

EVI fully complies with the demands of German General Accepted Accounting Principles (GAAP) and continuously empowers its staff working on projects to participate in budget control and the control of spending. For an organisation of its size, EVI does much more controlling than legally required to meet the highest standards. EVI operates an extensive continuous internal control system of financial management to meet the highest standards for public fund management. EVI diversifies its financial tasks and, despite its relatively small Secretariat, ensures the extensive and detailed control 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 to meet liquidity targets years in advance as part of risk management. Since July 2016, EVI introduced SAP Business by Design as the new accounting tool with fully integrated features same as the previous system in addition to many more features that are new. Thus adding to the excellency of EVI's financial and project management. The change of software was a challenge but has not made any difference to the presentations, which are as always true and fair financial presentations of EVI. During 2017 EVI perfectionized the SAP software and is planning further developments in 2018.

(b) Basis of accounting

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

One major basis of accounting that should be mentioned is that EVI retains the accounting treatment prescribed by International Accounting Standard (IAS) 20, namely recognise income up to the amount of expenditure allocated by government, the difference being recognised as deferred income.

The financial presentation in this report is based on the International Financial Reporting Standard (IFRS) as endorsed by the EU and is prepared in addition to the German GAAP & the German commercial code - Handelsgesetzbuch (HGB) statements which are the legal basis of the operation of the European Vaccine Initiative – EEIG.

The financial statements prepared in accordance with IFRS as endorsed by the EU include:

a) Statement of financial position

b) Statement of comprehensive income (activity based method)

c) Funds flow statement

d) Statement of changes in equity

e) Notes and additional performance report.

Negative amounts are shown within brackets as required by standard.

(c) Basis of preparation

The financial statements are presented in Euro (€), since the majority of EVI's activities are conducted in this currency (group functional and presentation currency). Fair value is the amount for which a financial asset, liability or instrument could be exchanged between knowledgeable and willing parties in an arm's length transaction.

The preparation of financial statements in conformity with German GAAP requires management to make judgements, estimates and assumptions that affect the application of policies and reported amounts of assets and liabilities, income and expenditure.

The estimates and associated assumptions are based on historical experience and various other factors that are believed to be reasonable under the circumstances. The results of which form the basis of making the judgements about carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates. If in the future such estimates and assumptions, which are based on management's best judgement at the date of the financial statements, deviate from the actual circumstances, the original estimates and assumptions will be modified as appropriate in the year in which the circumstances change.

(d) Funding parties

EVI is currently funded by Governmental agencies (Irish Aid, GHIT Fund) and the EU in addition to the EDCTP and privately by minor funding.

EVI is always open to new donors and other private funders, who share our vision of a world free of the burden of diseases of poverty or who perhaps want to support a good cause that combats poverty.

(e) Realised income policy

Public grants/donations received by EVI are posted on the balance sheet as deferred income. Grant-related expenditures are posted to the profit and loss (PNL), and –if eligible– are offset by corresponding amounts of income released from the deferred income. Only income generated from sales or other economic activity is directly recognised as income in the PNL.

An unconditional grant is recognised as revenue in the statement of comprehensive income when the grant becomes receivable. Any other grant which has performance, timing or other conditions is recognised in the statement of financial position as revenue once EVI has complied with the stipulated conditions. If the conditions have not yet been fully complied with, then this grant component is reported as a contingent asset as disclosed. They are considered as unrestricted funds, unless the donor stipulates a specific restriction. A reconciliation between donations received in cash and income recognised in the statement of comprehensive income is shown in note 6. Government grants are recognised as income for the allowable expenses incurred in the current year. At year end, the difference between the income recognised and the cumulative expenses incurred is accounted for as deferred income. When the donor wishes to see a donation allocated to a specific cause, the donation is considered to be an allocated fund. Allocated funds that have not been used at the end of the year are presented in a separate section of the statement of financial position.

(f) Contributions in kind

Occasionally EVI receives donations in kind, primarily in the form of free use of goods or services or preferential discounts and funds used at the premises of the lead investigator. These contributions in kind are not stated in the statement of comprehensive income as this type of contribution is difficult to valorise.

(g) Payables

All costs of EVI are charged to the PNL in the cost-relevant year on the basis of accrual based accounting. Payables are identified, evaluated and approved by the relevant project leaders for proof of deliverables and milestones. The Finance Unit then posts them accordingly to the respective accounts.

(h) Social mission expenditure

Social mission expenditures are expenses made in accordance with the purposes defined in EVI vision and mission.

Expenditures and grants allocated for R&D activities undertaken with the prospect of gaining new scientific or technical knowledge and understanding are recorded on the basis of contracts with grantees. In the event that a portion of a grant is unpaid at the year end, it is included under current liabilities. Expenses paid before year end for the following period are recorded as deferred R&D commitments in current assets.

Regulatory and other uncertainties inherent in the development of new products in this sector preclude EVI from capitalising development costs.

(i) Investment income and interest receivable

Interests received on EVI funds are included in the PNL in the year for which it is receivable.

(j) Primary and secondary commerce

EVI's primary focus is to develop vaccines against diseases of poverty. As a secondary activity, EVI may offer services and products in the form of lecturing, workshops and debates where needed as well as utilising to the full extent any surplus of products available.

(k) 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 EU/EDCTP and other similar projects.

(l) Time recording

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

(m) 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 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.

The annual work plan and budget are approved by the EVI-EEIG Board. They include funding for projects subcontracted to partners and current expenditures required to achieve the objectives for the year. Budget revisions are approved by the EVI-EEIG Board on an ad-hoc basis. All expenditures incurred on behalf of a project or for any EVI activity are recorded on an accrual basis.

(n) Tangible fixed assets

Tangible fixed assets are presented as the acquisition cost less accumulated depreciation. Depreciation is charged to the statement of operations on a straight-line basis over the estimated useful lives of the tangible fixed assets.

(o) Credit risk, cash-flow management

EVI's liquid assets are maintained in low-risk short- term deposits. At the balance sheet date, there are no significant concentrations of credit risk. The maximum exposure is primarily represented by the carrying amounts of the financial assets in the balance sheet, including accounts receivable and cash.

(p) Provisions

A provision is recognised on the balance sheet when the organisation has a legal or constructive obligation as a result of a past event, and it is probable that an outflow of economic benefits will be required to settle the obligation.

Provisions are measured according to the management's best estimates of the expenditure required to settle that obligation on the balance sheet date.

(q) Equity

Funds held by EVI as equity:

Equity is utilised as a strategic reserve for R&D by the organisation. EVI does not pay out any dividends or similar benefits to its shareholders as stipulated by the statutes of the organisation.

(r) 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 an exchange rate of 7.45. Monetary assets and liabilities denominated in foreign currencies at the statement of financial position date are translated to EUR at the foreign exchange rate ruling at that date. Foreign exchange differences arising on translation are recognised in the statement of comprehensive income. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate at the date of the transaction. EVI has, for the year 2017, made use of the following currencies: EUR, DKK, INR, USD, JPY, GBP and XOF.

(s) Financial auditors

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

The auditor issues an annual financial 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 an analysis of EVI and relevant recommendations by the auditor.

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

In addition, EVI has out-sourced its internal control to Prentis & Co, Cambridge, UK.

Note 2

Tangible fixed assets (EUR)	
Net carrying amount 31/12/2016	
Cost at beginning of the period 01/01/2016	25,834.70
Additions	17,271.33
Disposals	0.00
Cost at end of the period 31/12/2016	43,106.03
Accumulated amortisation 01/01/2016	0.00
Depreciation/amortisation expense 2016	18,127.03
Net carrying amount end of the period 31/12/2016	**24,979.00**
Net carrying amount 31/12/2017	
Cost at beginning of the period 01/01/2017	24,979.00
Additions	0.00
Disposals	0.00
Cost at end of the period 31/12/2017	24,979.00
Accumulated amortisation 01/01/2017	0.00
Depreciation/amortisation expense 2017	9,575.00
Net carrying amount end of the period 31/12/2017	**15,404.00**

Note 3

Creditors (EUR)	2017	2016
Creditors for grant linked payments	190,246.16	1,037,777.00
Other creditors	18,558.07	51,746.04
Total	**208,804.23**	**1,089,523.04**

Note 4

Accrued expenses (EUR)	2017	2016
Accrued paid leave	63,928.17	88,318.31
Accrued payables (grants linked)	566,518.81	1,783,431.77
Accrued direct costs	50,025.82	37,750.42
Accrued indirect costs	71,203.08	65,701.91
Accrued other expenses	3,730.37	3,730.37
Total	**755,406.25**	**1,978,932.78**

Note 5

Other liabilities (EUR)

Carrying period as per 31/12/2016	
Tax provisions	18,433.21
Social charges provisions	45,311.85
Other provisions	28,436.39
Total provisions 31/12/2016	**92,181.45**

Carrying period as per 31/12/2017	
Tax provisions	23,078.91
Social charges provisions	3,537.68
Other provisions	2,914.26
Total provisions 31/12/2017	**29,530.85**

Note 6

Deferred income

Cumulative donations committed to EVI as of 31 December 2017 and current deferred income

Donors	Contract currency	Total commitment in currency	Total commitment in euro	Deferred income 31-12-2016	Income as per statement of operations	Costs as per statement of operations	Deferred income 31-12-2017
Irish Aid - IE	EUR	6,000,000.00	6,000,000.00	**0.00**	500,000.00	500,000.00	**0.00**
GHIT - JP	JPY	757,115,556.00	5,797,209.46	**977,260.98**	2,785,948.37	3,271,165.94	**492,043.41**
FP7 - EU	EUR	16,229,077.00	16,229,077.00	**(358,216.59)**	1,063,303.20	1,231,303.38	**(526,216.77)**
H2020 – EU	EUR	15,518,071.00	15,518,071.00	**293,142.33**	3,709,997.55	3,442,769.18	**560,370.70**
EDCTP	EUR	8,674,445.17	8,674,445.17	**0.00**	0.00	0.00	**0.00**
IMI	EUR	8,000,000.00	8,000,000.00	**148,810.85**	969,691.26	937,168.59	**181,333.52**
Nobelpharma	USD	256,277.04	177,357.38	**256,277.04**	0.00	256,277.04	**0.00**
EVI reserve funds	EUR	3,321,642.18	3,321,642.18	**1,105,741.99**	0.00	227,622.90	**878,119.09**
Total			**63,717,802.19**	**2,423,016.60**	**9,028,940.38**	**9,866,307.03**	**1,585,649.95**

Deferred income

(b) Balance overview of grants and reserves (EUR)

Donator/Grant	Type	Balance 31/12/2016	Payments Received 2017	Cost allocated 2017	Balance 31/12/2017
IE Irish Aid	Core	**0.00**	500,000.00	500,000.00	**0.00**
EVI Reserve Funds	Core	**1,105,741.99**	0.00	227,622.90	**878,119.09**
JP GHIT /LEISHDNAVAX	Restricted	**0.00**	2,785,948.37	2,709,285.26	**76,663.11**
JP GHIT /SEmalvac	Restricted	**(73,143.66)**	0.00	48,980.11	**(122,123.77)**
JP GHIT /MVDvax	Restricted	**(30,156.53)**	0.00	(30,156.53)	**0.00**
JP GHIT /SEmalvac2	Restricted	**1,080,561.17**	0.00	543,057.10	**537,504.07**
EU EDUFLUVAC	Restricted	**45,557.11**	1,003,792.88	1,302,865.67	**(253,515.68)**
EU BELLEROPHON	Restricted	**(103,560.31)**	2,602.29	(100,958.02)	**0.00**
EU PlacMalVac	Restricted	**(99,705.43)**	56,908.03	(42,797.40)	**0.00**
EU TRANSVAC 2	Restricted	**0.00**	3,709,997.55	3,398,199.03	**311,798.52**
EU MuItiMalVax	Restricted	**(200,507.96)**	0.00	72,193.13	**(272,701.09)**
EU ZIKAVAX	Restricted	**293,142.33**	0.00	44,570.15	**248,572.18**
IMI FLUCOP	Restricted	**33,070.98**	13,402.54	17,613.93	**28,859.59**
IMI VAC2VAC	Restricted	**115,739.87**	956,288.72	919,554.66	**152,473.93**
NobelPharma/SEmalvac	Core	**256,277.04**	0.00	256,277.04	**0.00**
EVI Equity Reserves	Core	**1,987,299.95**	243,864.57	0.00	**2,231,164.52**
Total core		**3,349,318.98**	**743,864.57**	**983,899.94**	**3,109,283.61**
Total restricted		**1,060,997.57**	**8,528,940.38**	**8,882,407.09**	**707,530.86**
Total EVI funds		**4,410,316.55**	**9,272,804.95**	**9,866,907.03**	**3,816,814.47**

Note 7 - Income/realised (In EUR)

Funding used per project (restricted and unrestricted)

	GHIT & Irish Aid	EU	IMI	EDCTP
EVI vaccine development projects	3,241,428.24	0.00	0.00	0.00
Supportive EVI development costs	0.00	0.00	0.00	0.00
EU R&D projects	0.00	4,967,535.60	0.00	0.00
Supportive EU development costs	0.00	0.00	0.00	0.00
IMI R&D projects	0.00	0.00	938,410.61	0.00
Supportive IMI development costs	0.00	0.00	0.00	0.00
EDCTP R&D projects	0.00	0.00	0.00	0.00
Supportive EDCTP development costs	0.00	0.00	0.00	0.00
Executive administration	0.00	0.00	0.00	0.00
Internal allocations	0.00	0.00	0.00	0.00
Total income	**3,241,428.24**	**4,967,535.60**	**938,410.61**	**0.00**

	Reserves funds	Total income per activity	Overheads and interest	Total income
EVI vaccine development projects	4,062.37	3,245,490.61	0.00	3,245,490.61
Supportive EVI development costs	226,901.39	226,901.39	0.00	226,901.39
EU R&D projects	0.00	4,967,535.60	0.00	4,967,535.60
Supportive EU development costs	26,032.44	26,032.44	0.00	26,032.44
IMI R&D projects	0.00	938,410.61	0.00	938,410.61
Supportive IMI development costs	1,401.93	1,401.93	0.00	1,401.93
EDCTP R&D projects	0.00	0.00	0.00	0.00
Supportive EDCTP development costs	11,304.14	11,304.14	0.00	11,304.14
Executive administration	126,641.59	126,641.59	0.00	126,641.59
Internal allocations	0.00	0.00	243,864.57	243,864.57
Total income	**396,343.86**	**9,543,718.31**	**243,864.57**	**9,787,582.88**

Note 8

Social & non-social mission expenditure (EUR)	Notes	2017	2016
EVI vaccine development projects			
P27A	(a)	0.00	65,295.81
AMA1-DiCo	(a)	0.00	10,806.85
PlacID	(a)	0.00	238,260.52
PAMCPH	(a)	0.00	54,884.28
PRIMALVAC	(a)	0.00	777,835.97
MVDvax	(a)	34,487.56	14,013.29
SEmalvac	(a)	54,284.50	400,699.83
SEmalvac 2	(a)	543,057.10	16,042.84
LEISHDNAVAX	(a)	2,614,903.47	0.00
Supportive vaccine development costs	(a)	226,901.39	416,200.75
Total EVI vaccine development projects	**(a)**	**3,473,634.02**	**1,841,834.82**
EU-funded R&D projects			
Multimalvax		72,193.13	112,163.56
Placmalvac		149,707.62	91,684.22
Bellerophone		0.00	224,421.77
Edufluvac		1,302,865.67	135,824.78
Zikavax		44,570.15	2,083,957.46
Iprove		0.00	1,334.02
Transvac 2		3,398,199.03	0.00
Supportive project development costs		26,032.44	52,828.40
Total EU funded research and development projects		**4,993,568.04**	**2,702,214.21**
IMI funded R&D projects			
VAC2VAC		919,554.66	1,991,738.16
FLUCOP		17,613.93	13,112.62
Supportive project development costs		1,401.93	1,910.06
Total IMI funded R&D projects		**938,570.52**	**2,006,760.84**
EDCTP funded R&D projects			
MVVC		0.00	244,440.02
Supportive project development costs		11,304.14	29,222.45
Total EDCTP funded R&D projects		**11,304.14**	**273,662.47**
Executive administration			
Executive administrative management cost		126,641.59	458,847.09
Total executive administration		**126,641.59**	**458,847.09**
Total of all projects related expenditure	**(b)**	**9,543,718.31**	**7,283,319.43**

(a) Breakdown of R&D coordination expenditure per activity (EUR)	2017	2016
1 - Project development	168,960.73	435,737.24
2 - Process development	705.54	4,224.86
3 - Production	1,192.77	290,399.87
4 - Clinical trials	3,212,881.72	666,576.40
5 - Other support services	0.00	1,018.96
6 - International collaboration	88,067.93	17,533.83
7 - Quality Assurance	1,825.33	10,142.91
TOTAL	**3,473,634.02**	**1,425,634.07**

(b) Breakdown R&D coordination expenditure for preclinical and clinical activities costs per purpose in 2017 – value of above €5,000

Projects	Partners	Expenditure 2017
SEmalvac	CNRFP	17,324.99
SEmalvac 2	IRSS	429,996.66
SEmalvac 2	OSAKA UNIVERSITY	65,940.59
SEmalvac 2	PHARMALYS	12,860.35
LEISHDNAVAX	MOLOGEN	2,183,862.49
LEISHDNAVAX	NAGASAKI UNIVERSITY	191,679.01
LEISHDNAVAX	CHARITE	229,570.75
TRANSVAC2	25 European partners	3,271,046.10
VAC2VAC	13 European partners	786,236.24
EDUFLUVAC	5 European partners	838,760.45

(c) Presentation of EVI expenditures per nature of expenses (EUR)	2017	2016
Payables - EVI program related	3,164,761.52	1,070,009.18
Payables - EDCTP program related	0.00	244,440.02
Payables – EU & IMI program related	4,896,042.79	3,901,410.33
Salary costs (also includes in house consultants)	1,035,804.54	1,329,316.36
Contract service expenses	91,273.92	209,551.37
Facility & equipment maintenance expenses	76,439.74	112,803.37
Equipment, hardware & software	9,575.00	18,127.03
Travel & meetings expenses	116,717.88	182,335.57
Other direct expenses	(11,303.22)	16,039.10
Indirect business expenses	159,584.97	186,020.02
Board, BoS and SAC expenses	4,408.29	10,791.47
EU ISAC, SAC and SC expenses	412.88	2,475.61
Total expenses	**9,543,718.31**	**7,283,319.43**

Note 9

EVI stock of vaccine and adjuvant vials (non-accounted stock value)

Inventory ID	Name	Product type	Description	Batch number	Stock 01/01/17	Changes 2017	Quantity 31/12/17
NOVALABS	ALMy001	P27A vaccine	P27A Line A	ALMy001	703	(0)	703
NOVALABS	ALMy001	P27A vaccine	P27A Line B	ALMY001	822	(0)	822
NOVALABS	EVIy002	AMA1 - DiCo vaccine	pfAMa1 DiCo 60 µg lyophilised	EVIy002	904	(0)	904
NOVALABS	EVIy003	Adjuvant	Alhydrogel Line A	EVIy002	1,222	(0)	1,222
NOVALABS	EVIy003	Adjuvant	Alhydrogel Line B	EVIy002	1,390	(0)	1,390
NOVALABS	EVIc001	Adjuvant	Alhydrogel Line A	EVIc001	1,748	(-11)	1,737
NOVALABS	EVIc001	Adjuvant	Alhydrogel Line B	EVIc001	1,805	(0)	1,805

Independent auditor's report

To: European Vaccine Initiative EWIV, Heidelberg

We have reviewed the accompanying Statement of Financial Position, the Statement of Comprehensive Income, the Funds Flow Statement and the Statement of Changes in Equity as well as certain Notes to the Financial Presentation, (together "the Financial Presentation") of European Vaccine Initiative EWIV as at December 31, 2017.

Management's Responsibility for the Financial Presentation

Management is generally responsible for the preparation and fair presentation of German GAAP financial statements. In addition to German GAAP, management chose to prepare this Financial Presentation in accordance with IFRS as endorsed by the EU and as such remains also responsible for the preparation and fair presentation of this IFRS Financial Presentation and for such internal control as management determines is necessary to enable the preparation of the financial presentation that is free from material misstatement, whether due to fraud or error.

Auditor's Responsibility

Our responsibility is to express an opinion on the German GAAP financial statement based on our audit. We conducted our audit in accordance with International Standards on Auditing. Those standards require that we comply with ethical requirements and plan and perform the audit to obtain reasonable assurance about whether the financial statement is free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statement. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statement, whether due to fraud or error. In making those risk assessments, the auditor considers internal control relevant to the entity's preparation and fair presentation of the financial statement in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates, if any, made by management, as well as evaluating the overall presentation of the financial statement.

We have issued a separate audit opinion on the German GAAP financial statements as at December 31, 2017 of European Vaccine Initiative EWIV, Heidelberg, dated March 29, 2018.

Our audit engagement also included the review of the accompanying Financial Presentation in accordance with IFRS as endorsed by the EU.

We believe that the evidence we have obtained in connection with the review of the accompanying Financial Presentation in accordance with IFRS as endorsed by the EU is sufficient and appropriate to provide a basis for our opinion.

Opinion

In our opinion, the Financial Presentation presents fairly, in all material respects, the financial position of European Vaccine Initiative EWIV as at December 31, 2017 in accordance with IFRS as endorsed by the EU relevant to preparing such Financial Presentation.

Heidelberg, March 29, 2018

FALK GmbH & Co KG
Wirtschaftsprüfungsgesellschaft
Steuerberatungsgesellschaft

(Meyer)
Wirtschaftsprüfer

(Ahrens)
Wirtschaftsprüfer

List of abbreviations

	3D7	*Plasmodium falciparum* clone 3D7
A	**ADCI**	Antibody-Dependent cellular Inhibition
	AMA1	Apical Membrane Antigen 1
	AS01$_B$	GSK Biologicals' Adjuvant System AS01$_B$
	AS02$_A$	GSK Biologicals' Adjuvant System AS02$_A$
	ASTMH	American Society for Tropical Medicine and Hygiene
B	**BK-SE36**	*Plasmodium falciparum* serine repeat antigen-5 formulated with aluminium hydroxyl gel
	BMBF	German Federal Ministry of Education and Research
	BMGF	Bill & Melinda Gates Foundation
	BoS	Board of Stakeholders
	BPRC	Biomedical Primate Research Centre
C	**CEA**	Commissariat à l'énergie atomique et aux énergies alternatives
	ChAd	Chimpanzee Adenovirus
	CHUV	Centre hospitalier universitaire vaudois
	CIC	Centre d'investigation clinique
	CNRFP	Centre national de recherche et de formation sur le paludisme
	CpG	Cytosine triphosphate deoxynucleotide phosphodiester link to Guanine triphosphate deoxynucleotide DNA
	CSA	Chondroitin Sulfate A
	CSP	Circumsporozoite Protein
D	**DBL**	Duffy-Binding-Like
	DGIS	Directorate General for International Cooperation at Ministry of Foreign Affairs, The Netherlands
	DiCo	Diversity Covering
	DK	Denmark
	DNA	Deoxyribonucleic Acid
	DSMB	Data Safety Monitoring Board
	DSW	Deutsche Stiftung Weltbevölkerung
E	***E. coli***	*Escherichia coli*
	EDCTP	European and Developing Countries' Clinical Trials Partnership
	EDQM	European Directorate for the Quality of Medicines & HealthCare
	EDUFLUVAC	Educate Influenza Vaccine
	EEIG	European Economic Interest Grouping
	EFPIA	European Federation of Pharmaceutical Industries and Associations
	EKUT	Eberhard Karls Universität Tübingen
	ELISA	Enzyme-Linked Immunosorbent Assay
	ELISpot	Enzyme-Linked ImmunoSpot Assay
	EMA	European Medicines Agency
	EPI	Expanded Programme on Immunization
	EU	European Union
	EVI	European Vaccine Initiative

F	**Fraunhofer IME**	Fraunhofer Institute for Molecular Biology and Applied Ecology
	FRMC	Financial Risk Management Committee
G	**GAAP**	German General Accepted Accounting Principles
	GHIT	Global Health Innovation Technology
	GIA	Growth Inhibition Assay
	GLA	Glucopyranosyl Lipid A Adjuvant-Stable Emulsion
	GM	The Gambia
	GMP	Good Manufacturing Practice
	GMZ2	Recombinant *Lactococcus lactis* hybrid glutamate-rich protein and merozoite surface protein 3
	GSK	GlaxoSmithKline
H	**HA**	Haemagglutinin
	HTF	Danish National Advanced Technology Foundation
I	**IAS**	International Accounting Standard
	IB	Investigator's Brochure
	iBET	Instituto de Biologia Experimental e Tecnológica
	IDRI	Infectious Disease Research Institute
	IE	Republic of Ireland
	IFRS	International Financial Reporting Standard
	IHI	Ifakara Health Institute
	IMI	Innovative Medicines Initiative
	IMPD	Investigational Medicinal Product Dossier
	IMX	Tag developed by IMAXIO
	Inserm	Institut national de la santé et de la recherche médicale
	Intravacc	Institute for Translational Vaccinology
	INTS	Institut national de transfusion sanguine
	IPP	Institut Pasteur Paris
	IPROVE	Innovation Partnership for a Roadmap on Vaccines in Europe
	IR	Ireland
	IRD	Institut de recherche pour le développement
	IRSS	Institut de Recherche en Sciences de la Santé
K	**kDa**	Kilodalton
	KEMRI	Kenya Medical Research Institute
	KfW	Kreditanstalt für Wiederaufbau
	KHRC	Kintampo Health Research Centre
L	**LMIC**	Low- and Middle-Income Countries
	LMIV	Laboratory of Malaria Immunology and Vaccinology
	LSHTM	London School of Hygiene & Tropical Medicine
	LSQ	Liposome-QS21 formulation

M	**Matrix M**	Adjuvant by Novavax, in which matrix complexes are formed by a specific mixture of Quillaja saponin, cholesterol and phospholipids
	ME-TRAP	Multiple Epitope Thrombospondin-Related Adhesion Protein
	MHRA	Medicine and Healthcare Products Regulatory Agency
	MN	MicroNeutralisation virus assay
	MPL	Monophosphoryl Lipid A
	MRC	Medical Research Council
	MSc	Master of Science
	MSP	Merozoite Surface Protein
	MultiMalVax	Multi-stage Malaria Vaccine
	MV	Measles Vector
	MVA	Modified Vaccinia Virus Ankara
	MVDVax	Measles Virus Dengue Vaccine
	MVI	Malaria Vaccine Initiative
	MVVC	Malaria Vectored Vaccines Consortium
	MVVC2	Malaria Vectored Vaccines Consortium 2
N	**NA**	Neuraminidase
	NEKKEN	Institute of Tropical Medicine Nagasaki University
	NGO	Non-governmental organisation
	NHP	Non-Human Primates
	NIBSC	National Institute for Biological Standards and Control
	NIH/NIAID	National Institutes of Health/National Institute of Allergy and Infectious Diseases
O	**ODN**	Oligodeoxynucleotides
	OMCL	Official Medicines Control Laboratories
	OPTIMALVAC	Initiative on Optimising Malaria Vaccine laboratory assay evaluation
P	**P27A**	Fragment P27A of PFF0165c malaria protein
	PAMCPH	Recombinant VAR2CSA protein as a vaccine candidate for pregnancy-associated malaria
	PCR	Polymerase Chain Reaction
	PDP	Product Development Partnership
	PEI	Paul-Ehrlich Institute
	Pf	*Plasmodium falciparum*
	PfAMA1	*Plasmodium falciparum* Apical Membrane Antigen 1
	PfEBA-175	*Plasmodium falciparum* Erythrocyte-Binding Antigen-175
	PfEMP1	*Plasmodium falciparum* Erythrocyte Membrane Protein-1
	PfMSP	*Plasmodium falciparum* Merozoite Surface Protein
	PfRH5	*Plasmodium falciparum* Reticulocyte-binding protein Homologue 5
	PhD	Doctor of Philosophy
	PIM	Paratyphoid Infection Model
	PlacID	Modelling Placental Infection and Disease
	PlacMalVac	Clinical development of a VAR2CSA-based placental malaria vaccine candidate
	PNL	Profit and Loss
	PPC	Preferred Product Characteristics
	PRIMALVAC	Recombinant VAR2CSA protein as vaccine candidate for placental malaria

R	**R&D**	Research and Development
	R21	Circumsporozoite protein particle
	RI	Research Infrastructure
	RIMD	Research Institute for Microbial Diseases
	RIVM	National Institute for Public Health and the Environment
	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
S	**SAC**	Scientific Advisory Committee
	SE	Stable Emulsion
	SE36	*Plasmodium falciparum* serine repeat antigen 5 N-terminal domain
	SEmalvac	Serine repeat antigen-5 malaria vaccine
	SERA5	Serine Repeat Antigen-5
	Sida	Swedish Development Agency
	SMEs	Small and Medium Enterprises
	SN	Senegal
	SP	Spain
	Swiss TPH	Swiss Tropical and Public Health Institute
T	**TLR**	Toll-Like Receptor
	TRANSVAC	European Network of Vaccine Research and Development
U	**UAC**	Université d'Abomey-Calavi
	UCAD	Université Cheikh Anta Diop
	UCPH	University of Copenhagen
	UK	United Kingdom
	UNIL	University of Lausanne
	UOXF	University of Oxford
	UPMC	Université Pierre et Marie Curie
V	**VAC2VAC**	Vaccine batch to vaccine batch comparison by consistency testing
	Var	Genes encoding the PfEMP-1 proteins
	VAR2CSA	Variant surface antigen that mediates adhesion of the infected erythrocyte to CSA
	VLP	Virus-like Particle
	VSCR	Vienna School of Clinical Research
W	**WBVR**	Wageningen Bioveterinary Research
	WP	Work Package
	WHO	World Health Organization

Acknowledgments

EVI would like to thank all partners, funders, participants in EVI-funded clinical trials and projects, and all other individuals and organisations who have supported EVI since the very beginning. The resources mobilised to date have allowed EVI to support during our nearly 20 years of existence further research and development related to 35 different vaccine candidates for diseases and pathogens as diverse as malaria, leishmaniasis, influenza, Zika, dengue and others. All in all, EVI has secured with our partners almost 180 million euros for the benefit of the scientist and the development of vaccines. We gratefully acknowledge the funding and other kinds of support to EVI from the following organisations that has allowed advancing our mission.

- Danida, Denmark's development cooperation, Denmark
- Department of Foreign Affairs, Irish Aid, Ireland
- Dutch Ministry of Foreign Affairs, Directorate-General for International Cooperation (DGIS), The Netherlands
- Dutch Research Council, The Netherlands
- European and Developing Countries Clinical Trials Partnership (EDCTP), The Netherlands, with co-funding from EU Member States and other countries
- European Union (EU), Belgium
- Federal Ministry of Education and Research (BMBF) through KfW, Germany
- Global Health Innovative Technologies (GHIT) Fund, Japan
- Innovative Medicines Initiative (IMI), Belgium
- Nobelpharma Co., Ltd., Japan
- Swedish Ministry of Foreign Affairs, Swedish International Development Cooperation Agency (Sida), Sweden
- World Health Organization - Special Programme for Research and Training in Tropical Diseases (WHO-TDR), Switzerland
- Minor donations and support though marketing and communications
  - All4Cloud
  - SAP
- Co-funding was kindly provided by the following organisations:
  - NIH – NIAID, United States of America
  - Research Institute for Microbial Diseases (RIMD), Japan
  - Kenya Medical Research Institute (KEMRI), Kenya
  - Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso
  - Université Cheikh Anta Diop (UCAD), Senegal
  - Medical Research Centre, The Gambia (MRC Gambia)
  - ReiThera s.r.l, Italy
  - University of Copenhagen, Denmark
  - Danish National Advanced Technology Foundation, Denmark
  - Inserm, France
  - Institut National de la Transfusion Sanguine (INTS), France
  - Centre National de la Recherche Scientifique (CNRS), France
  - Vienna School of Clinical Research (VSCR), Austria
  - Austrian Federal Ministry of Science and Research, Austria
  - University of Oxford, United Kingdom
  - Sanofi Pasteur (SP), France
  - Zoetis Belgium SA (Zoetis), Belgium
  - Merial, France
  - Boehringer Ingelheim (BI), Germany
  - Intervet International B.V., also known as MSD Animal Health (MSD), Netherlands
  - GSK Biologicals (GSKBio), Belgium

Partners

Abbott	NL
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Medical Research Council Uganda on behalf of its MRC/ UVRI Uganda Research Unit on AIDS	UG
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European Vaccine Initiative

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