PAMCPH & PlacMalVac

var2CSA as a Pregnancy Associated Malaria Vaccine Candidate

Women, who have acquired immunity against malaria during childhood, nevertheless become susceptible to malaria again during their first pregnancies. Pregnancy Associated Malaria (PAM) is caused by *Plasmodium falciparum*-infected erythrocytes that bind to the placental receptor Chondroitin Sulfate A (CSA) and sequester in the placenta, where they cause disease and death for the mother and her off-spring. Every year, PAM threatens more than 100 million pregnant women, causing the death of an estimated 10,000 women and up to 200,000 infants. Currently for PAM the only preventive strategies to improve maternal and fetal outcomes include intermittent preventive treatment (IPT) and insecticide-treated bed nets. However, resistance to drugs used for IPT by the parasite and waning efficacy of the bed nets due to insecticide resistance in the vector represent major threats, and vaccines against malaria do not exist to date. Fortunately, women can acquire immunity against PAM and this has raised hope that a vaccine for PAM can be developed.

Background

In 2003, var2CSA was identified at Centre for Medical Parasitology - University of Copenhagen - as the parasite protein responsible for the binding of infected erythrocytes to CSA in the placenta[1, 2]. Only women who have had placental malaria have antibodies against the var2CSA protein and give birth to healthier babies in comparison to women infected for the first time by placental malaria during their pregnancy. Since the interaction between var2CSA and CSA is a key element in the pathogenesis of PAM, a promising vaccination strategy is to induce antibodies that block the binding of parasitised erythrocytes to the placenta.

The existence of a reliable in vitro assay for the evaluation of the vaccine efficacy has now enabled researchers to define specific regions of var2CSA that can be used in an adhesion-blocking vaccine. Var2CSA is a complex 350kDa protein with seven large domains. Over the last years and with the support of different funding schemes, Ali Salanti's group has produced more than 200 different recombinant var2CSA antigens in different expression systems and assessed the capacity of Immunoglobulin G (IgG) induced by immunisation of animals to inhibit parasite binding to CSA. They have identified one subunit of the var2CSA protein (inter-domains ID1-ID2a encompassing Duffy Binding-Like (DBL2X) domain) that induces highly inhibitory and cross-inhibitory IgGs[3]. This subunit has already been successfully produced in small scale and at high yields in S2 cells at ExpreS2ion Biotechnologies.

Objectives

The overall objective of the PAMCPH and PlacMalVac projects is to provide proof of concept that a var2CSA based vaccine inducing long lasting or rapidly boosted cross reactive and inhibitory antibodies can be designed for preventing PAM and improve pregnancy outcomes in malaria endemic areas.

The PAMCPH project supports the process development, production under current Good Manufacturing Practice (cGMP) and pre-clinical assessment of a recombinant var2CSA fragment based vaccine. PAMCPH is funded by the Federal Ministry of Education and Research Germany (through Kreditanstalt für Wiederaufbau) and the Danish National Advanced Technology Foundation. The vaccine candidate will be used to conduct the phase I clinical trial supported by the PlacMalVac project, which is funded by the European Commission's Seventh Framework Programme.

PAMCPH & PlacMalVac

Vaccine Inventors

Ali Salanti and Thor Theander, Centre for Medical Parasitology, University of Copenhagen, Copenhagen, Denmark

Partners:

PAMCPH
University of Copenhagen, DK
Expres2ion Biotechnologies, DK
CMC Biologics, DK
PlacMalVac
University of Copenhagen, DK
Expres2ion Biotechnologies, DK
Institut de recherche pour le développement, FR
Université d'Abomey-Calavi, BEN
University of Tübingen, DE

Total budget:

PAMCPH € 2,000,000
PlacMalVac € 5,934,981

Project Duration:

PAMCPH: 48 months
PlacMalVac: 36 months

Start date:

PAMCPH: 1 December 2011
PlacMalVac: 1 March 2013

Funding:

SPONSORED BY THE
Federal Ministry of Education and Research
through KFW
The Danish National Advanced Technology Foundation
EUROPEAN COMMISSION
UNIVERSITY OF COPENHAGEN

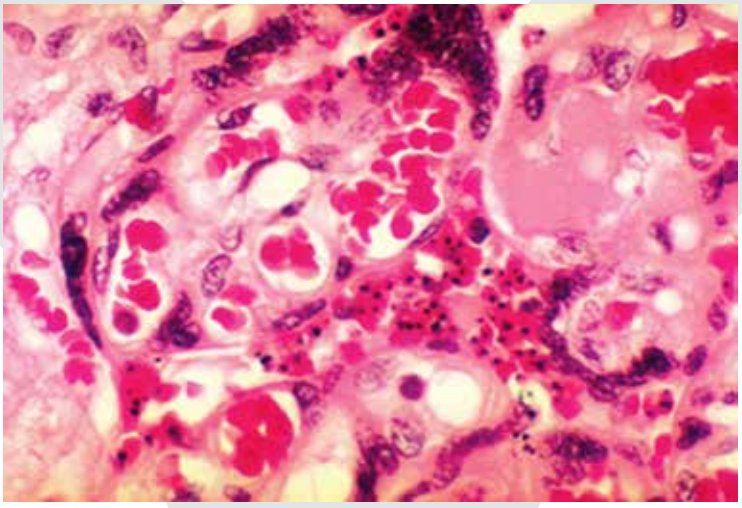
Major Milestones

PAMCPH

- Research cell banks of 2-3 clones generated and tested
- GMP process development transferred to contract manufacturing organisation
- Drug substance cGMP batch release
- Drug product cGMP batch release
- Toxicology studies final report
- Investigational medicinal product dossier

PlacMalVac

- Definition of the optimal protein adjuvant formulation for the clinical trials
- Optimisation of the production of the vaccine antigen
- Protocol of the phase I clinical trial
- Phase I clinical trial approval by regulatory authorities and independent ethic committees
- Definition of the end-points of efficacy and the number of subjects required for the phase II clinical trial.



A photomicrograph of placental tissue revealing the presence of the malarial parasite Plasmodium falciparum. http://phil.cdc.gov/phil/details.asp - Edwin P. Ewing, Jr., M.D

References

1. Salanti A, Mol Microbiol. 2003 Jul; 49(1):179-91.
2. Khunrae P, J. Mol. Biol. 2010 Apr; 397:826-834.
3. Clausen TM, J. Biol. Chem. 2012 May; 287(28):23332-23345.