The development of a Pregnancy Associated Malaria vaccine at the European Vaccine Initiative

African woman with her child (photo kindly provided by Roll Back Malaria).

Pregnancy Associated Malaria (PAM) is caused by *P. falciparum* infected Erythrocytes (PE) that bind to the placental receptor Chondroitin Sulphate A (CSA) and sequester in the placenta[1], where they cause disease and death for the mother and her off-spring. Every year, more than 100 million pregnant women are threatened by PAM, which causes the death of 80,000 - 200,000 children[2]. 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. This problem has long been neglected, and no vaccine preventing PAM is available.

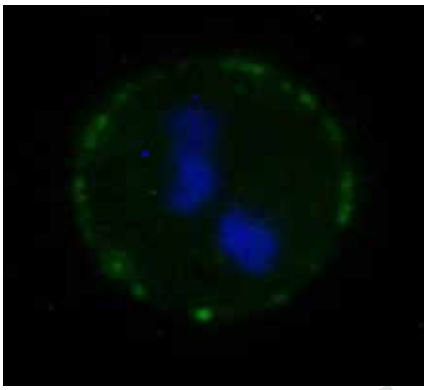
The European Vaccine Initiative (EVI) has been instrumental in the mobilisation of €16 million for the development of vaccines against PAM, through the German Federal Ministry of Education and Research (BMBF) funded projects **PRIMALVAC** and **PAMCPH** as well as the European Commission (EC) Framework Programme 7 funded project **PlacMalVac**. Dr Odile Leroy: "With these three projects EVI has become the leading Product Development Partnership to advance the development of vaccines against pregnancy-associated malaria. These projects offer hope for reducing the burden of severe malaria in pregnant women and improving the health of mothers and new-borns".

Apart from the funding provided by the BMBF and the EC, the three projects receive major co-funding from Irish Aid (through EVI), the Institut national de la santé et de la recherche médicale (Inserm) and the Institut National de la Transfusion Sanguine (INTS), and additional contributions from the Universities of Copenhagen and Benin, the Danish National Advanced Technology, the Institut de Recherche pour le Développement (IRD), and by ExpreS2ion Biotechnologies, respectively. Moreover, in order to strengthen the network between the main groups working on a PAM vaccine, EVI has set up a collaboration with the United States – National Institutes of Health (NIH).

The three PAM projects focus on the distinct form of the parasite that infects the placenta, causing disease and death in mothers and infants. Evidence strongly supports var2CSA, a member of the PfEMP1 adhesins encoded by the var gene family, as the leading candidate for a PAM vaccine[3,4,5]. Indeed, var2CSA is preferentially expressed by placental parasites and the protein binds to CSA[6]. Women acquire antibodies against var2CSA expressed by placental parasites over successive pregnancies, as they become resistant to pregnancy malaria[7]. These data provide a rational basis for accelerating vaccine development aimed at blocking the adhesion of CSA-binding parasites to the placenta.

The target product profile of PAM vaccines notably differs from the currently developed malaria vaccine. PAM vaccines target young adolescent girls before childbearing age, and the vaccination could be associated to other vaccines targeting either prevention of rubella or prevention of uterine cervical cancer by Human papilloma virus vaccine. Depending on the other malaria vaccine available on the market, a PAM vaccine could potentially be associated with a booster dose of a regular malaria vaccine in adolescent girls.

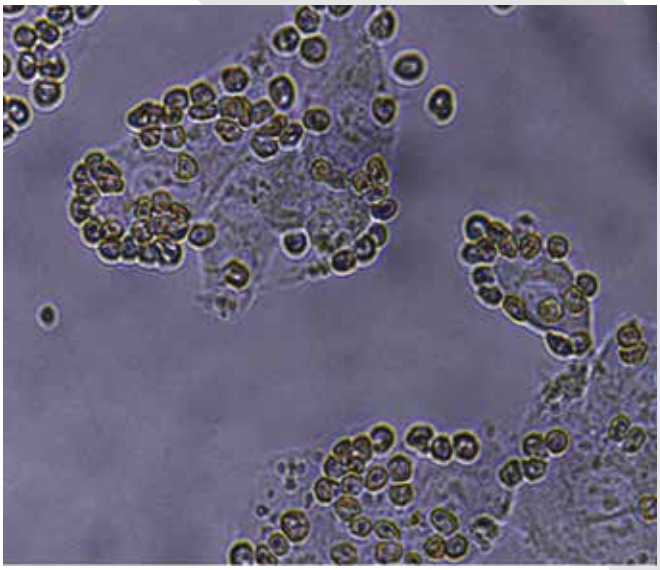
The PRIMALVAC project, whose vaccine inventor is Dr Benoit Gamain (Inserm, France), includes the transition of a var2CSA candidate antigen that best meet strict immunogenicity criteria to preclinical and clinical development. The PAMCPH project focusses on the production of another recombinant var2CSA vaccine candidate discovered by Prof Ali Salanti and Prof Thor Theander (University of Copenhagen, Denmark) under current Good Manufacturing Practice (cGMP).



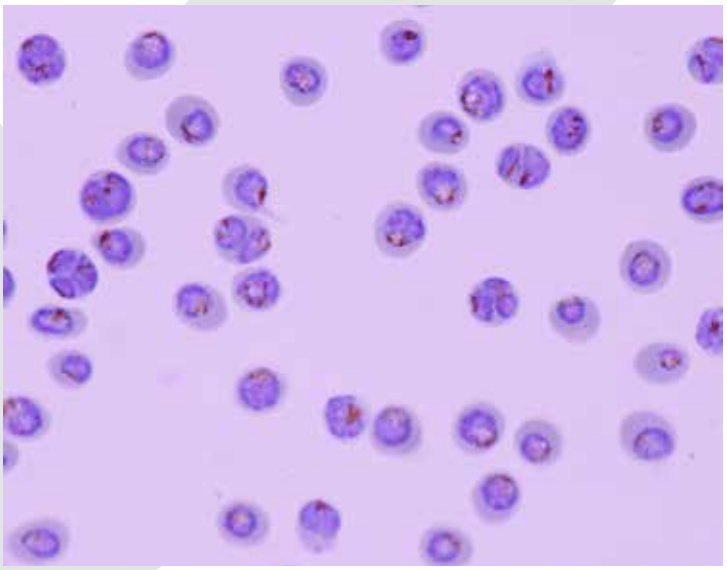
P. falciparum infected erythrocytes expressing var2CSA on their surface (in green). The parasite nuclei stained in blue. (photo kindly provided by Benoit Gamain, Inserm).

This vaccine candidate will be used in the phase I clinical trial supported by the PlacMalVac project, in collaboration with the five project partners (University of Copenhagen, IRD, Expres2ion Biotechnologies, EVI, Université d'Abomey-Calavi, and Eberhard Karls University Tuebingen). The main common objective of these projects is to obtain proof of concept that a var2CSA based vaccine inducing long lasting or rapidly boosted cross reactive and inhibitory antibodies can be designed for human use.

1. Fried M et al., Science. 1996 Jun 7;272(5267):1502-4.
2. Hartman TK et al., Annals of Tropical Paediatrics. 2010;30:271-282
3. Baruch DI et al., Cell. 1995 Jul 14;82(1):77-87
4. Su XZ et al., Cell. 1995 Jul 14;82(1):89-100
5. Smith JD et al., Cell. 1995 Jul 14;82(1):101-10.
6. Salanti A et al., Mol Microbiol. 2003 Jul;49(1):179-91.
7. Fried M et al., Nature. 1998 Oct 29;395(6705):851-2



Microscope photograph of erythrocytes infected with Chondroitin Sulfate A (CSA) binding parasites adhering to placental BeWo cells (human placental cell line that originates from a choriocarcinoma). (photo kindly provided by Benoit Gamain, Inserm).



Purified P. falciparum infected erythrocytes. (photo kindly provided by Nicola Viebig, EVI and Benoit Gamain, Inserm).