Clinical Development of Malaria Vaccine Candidate NPC-SE36

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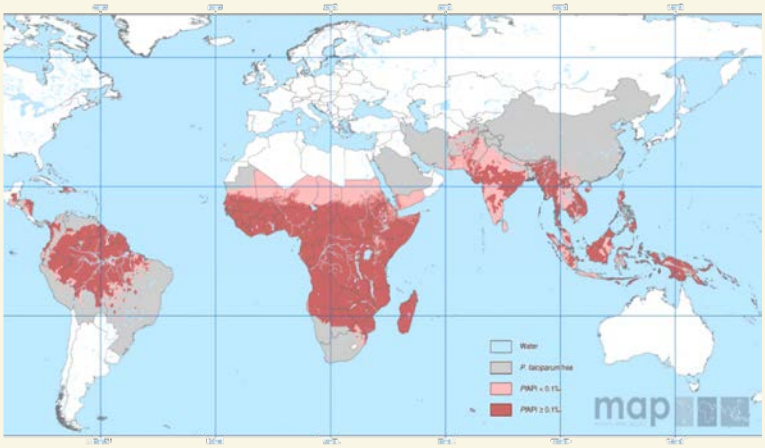
This vaccine candidate is under development.
Selling and Providing is definitely prohibited.

Malaria, a tropical disease transmitted by Anopheles mosquito, causes more than two hundred million clinical cases and over 400,000 deaths annually. Majority of the burden is in children under 5 years living in sub-Saharan African countries. Pregnant women in the same region also suffer from malaria and around 0.2 million infant deaths are attributable each year to malaria infection during pregnancy. This disease is a serious obstacle for economic development as well as public health.

Mothers in hospital holding babies with severe malaria



Malaria endemic regions

Global death due to malaria (1980 – 2016)

1980-2010

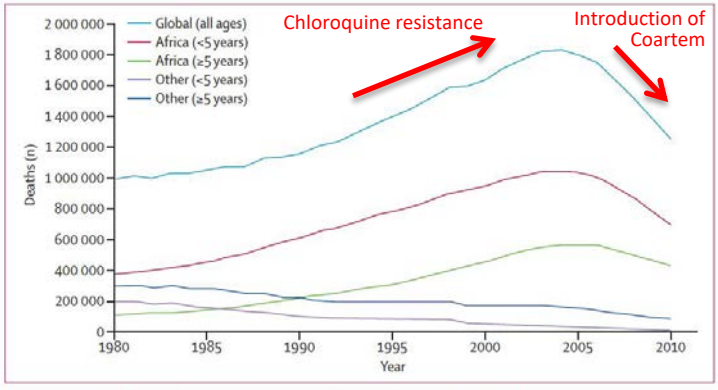
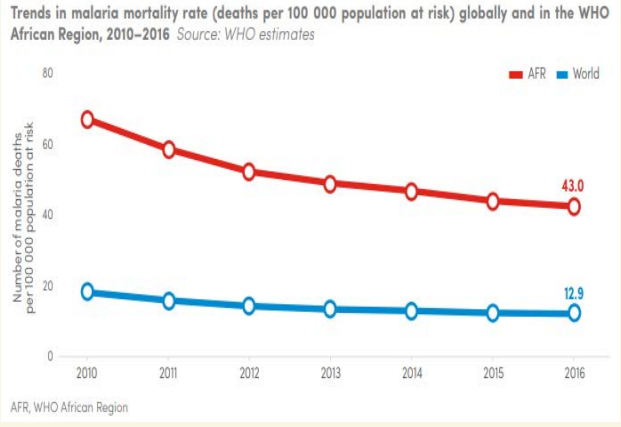


Figure 2: Trends in global malaria deaths by age and geographical region, 1980 to 2010

Murray et al., Lancet 2012; 379: 413–31

2010-2016



WHO World Malaria Report 2018

Rationale for Malaria Vaccine Development

Coartem remains efficacious in most malaria endemic areas but a combination of challenges, for example, unsustained sufficient funding for malaria control, limitation on the distribution/use of bednets and inadequate compliance to drugs treatment has contributed to stalling of malaria deaths in recent yaers (2015-2017). Antimalarial drugs and mosquito nets are not so desirable in terms of long term sustainability and resources and, thus, a vaccine would be an important health care tool.

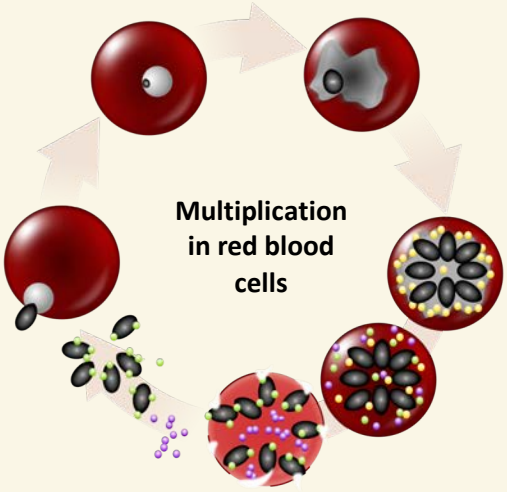
Malaria tropica Malaria Vaccine Candidate NPC-SE36

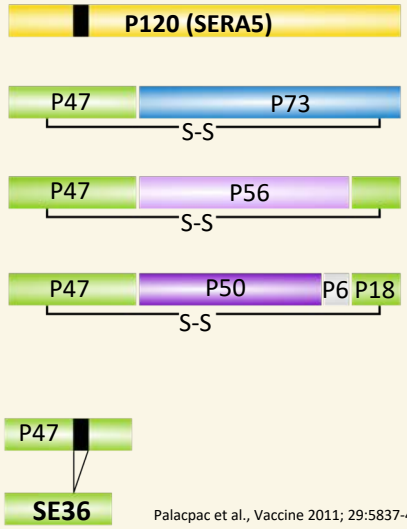
(Previously called BK-SE36)

SE36 is part of the SERA5 antigen. SERA5 is an essential protein expressed in blood-stage parasites. The NPC-SE36 is a lyophilized formulation of the vaccine antigen with aluminum hydroxide gel. Recombinant SE36 protein, is produced by *E. coli* by recombinant DNA technology. NPC-SE36 has excellent storage stability, being stable for 6 months at room temperature.
While the SE36 was also shown to contribute to the mechanism that camouflages merozoites from immune attack, the vaccination with SE36 protein also induces antibodies that attack malaria parasites.

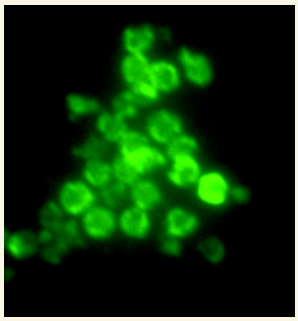
Since 2018, the malaria vaccine candidate BK-SE36 has been renamed NPC-SE36.

Molecular Structure of SERA5 and its Expression





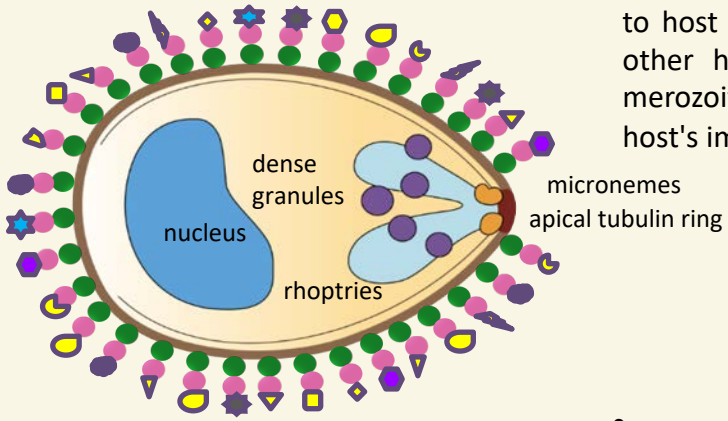
Palacpac et al., Vaccine 2011; 29:5837-45



Fluorescently labeled SE36 protein covers the surface of merozoites.

Li et al., Parasitol Int. 2002; 51:343-52.

Molecular Camouflage of P. falciparum Merozoite by Hijacking Host Proteins



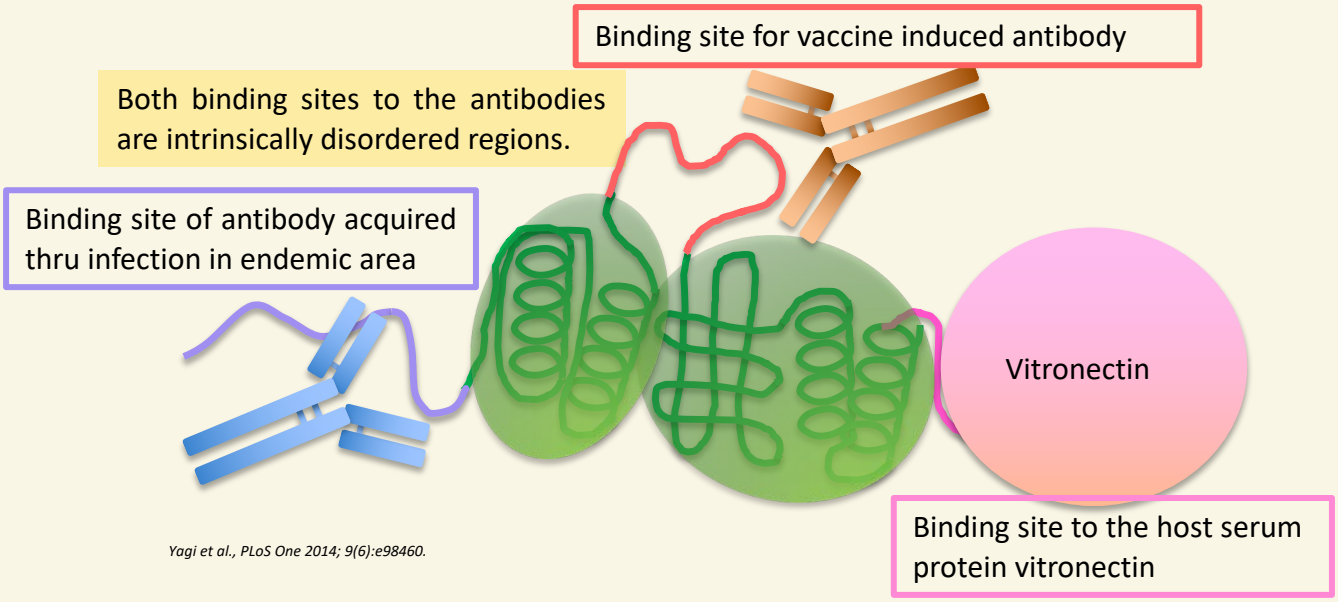
The SE36 protein on the merozoite surface binds to host vitronectin, which in turn binds to many other host proteins. Thus, the surface of the merozoite is covered with host proteins, and the host's immune cells do not recognize it as non-self.

Tougan et al., Sci Rep 2018; 5052

Advantages of the SE36 Protein as a Malaria Vaccine Antigen

Structure of SE36 protein molecule

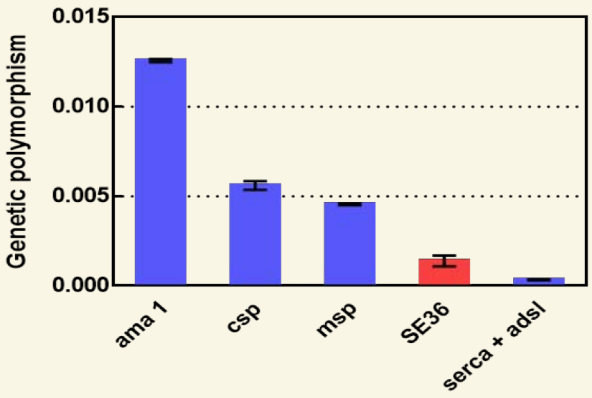
The SE36 protein is from the N-terminal region of SERA5 antigen. The molecular weight is 36 kDa, and the figure below is a prediction of its three-dimensional structure. Anti-SE36 antibodies acquired through natural infection from endemic residents serum binds to the left region, whereas anti-SE36 antibodies induced by NPC-SE36 vaccination binds to the central part. Both regions are intrinsically disordered regions and do not form a rigid structure or strict conformation. Since it does not have a three-dimensional structure, SE36 protein as an antigen does not require three-dimensional structure reconstruction to elicit protective antibodies and is excellent in thermostability.



Yagi et al., PLoS One 2014; 9(6):e98460.

Tougan et al., Sci Rep 2018; 5052

The sequence of the SE36 gene is well conserved



ama 1, csp, msp1; other vaccine candidate antigen genes
serca + adsl; house keeping genes

Comparison of 455 *Plasmodium falciparum* genes collected from all over the world

In general, the biggest problem in the development of a malaria vaccine is that the antigen gene exhibits high genetic polymorphism. In endemic areas, strains having identical sequence to the vaccine antigen(s) are uncommon and this affects vaccine efficacy, resulting to poor or no protection to genotypes present in the field. On the other hand, the SE36 gene is extremely well conserved as glimpse from *P. falciparum* amino acid sequences collected from all over the world. Thus, the promising results are expected to be replicated widely.

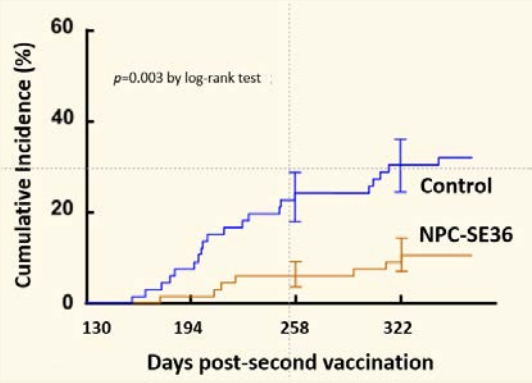
Tanabe et al., Vaccine 2012; 30:1583-93.
Tanabe et al., Vaccine 2013; 31:1334-9.

Clinical Trial and Follow-up Research of the Malaria Vaccine Candidate NPC-SE36 in Uganda

With approval from Uganda national Council for Science and Technology, a clinical trial was conducted in compliance with Good Clinical Practices from 2010 to 2011. After safety assessment in men and women above 21 years old, vaccination in 6-20 years old volunteers were carried out and a follow-up research was conducted to further monitor malaria incidences and health for a year.

Malaria Vaccine Candidate NPC-SE36

The follow-up research was done on NPC-SE36 vaccinees aged 6-20 years old (66 people) and control volunteers (66 people). It was observed that overall the number of incidences of high parasitemia and fever in the vaccine group was less than those in the control group with promising protective efficacy of 72% (p=0.003).



Palacpac et al., PLoS One 2013; 8(5):e64073.

Other Malaria Vaccine Candidates

RTS,S/AS01A Vaccine developed by GSK（Glaxo Smith Klein）

Vaccine efficacy against clinical malaria:
5-17 month-old volunteers = 36.3%
6-12 week-old volunteers = 25.9%
over a median follow-up of 38 and 48 months from first vaccine dose.

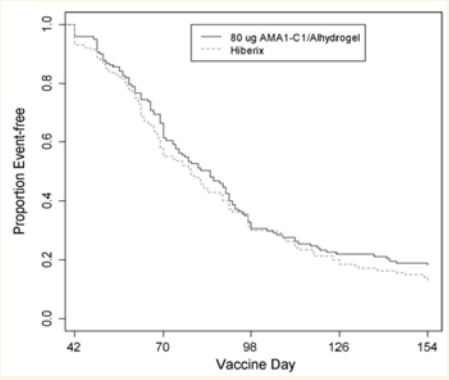
Vaccine efficacy against severe malaria:
5-17 month-old = 32.2%
6-12 week-old = 17.3%

Not yet licensed, a large scale implementation study is now in place to confirm protective efficacy using 4 doses and assess several safety signals seen in phase 3 trial.

RTS,S Clinical Trials Partnership, The Lancet 2015; 386:31–45.
Global Advisory Committee on Vaccine Safety, 7–8 June 2017

AMA1-C1/Alhydrogel Vaccine developed by NIAID, NIH, USA

After two vaccinations, the half-year protective effect was 0%. Vaccine development has been stopped but clinical research continues.



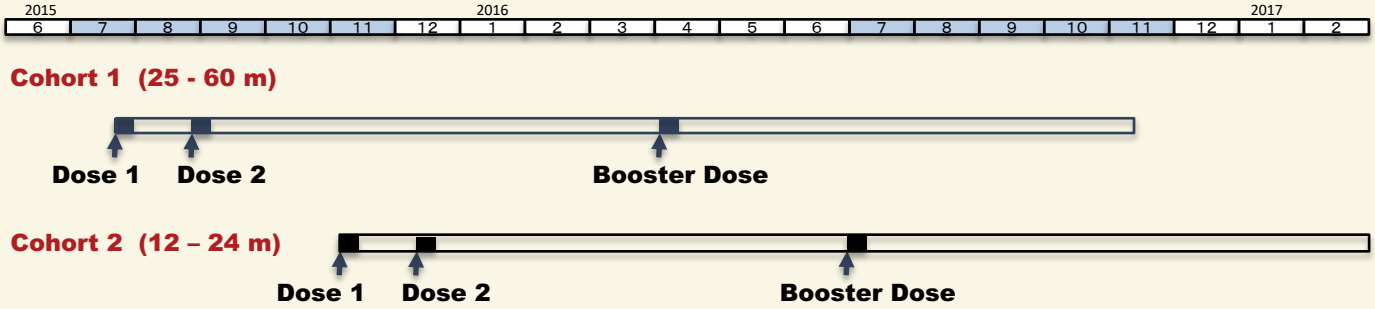
Sagara et al., Vaccine 2009; 27:3090-8.
Mata et al., Biomed Res Int 2013; 2013:282913.

Clinical Trial of the Malaria Vaccine Candidate NPC-SE36 in 1-5 year-old Children in Burkina Faso (Phase Ib)

Since the target age group for malaria vaccine in endemic areas, as recommended by WHO, are children under 5 years of age, we conducted vaccine safety studies in 1-year-old children. In collaboration with the European Vaccine Initiative (Heidelberg, Germany) and the Burkina Faso National Center for Malaria Research, Phase Ib clinical trial (1-5 years old) of NPC-SE36 started in June 2015 and ended in February 2017. The vaccine was well tolerated.

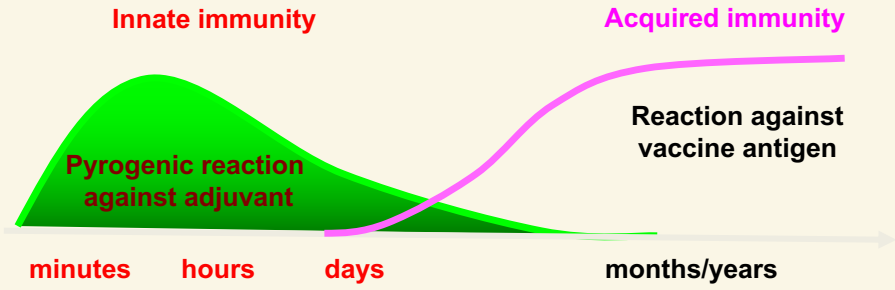
The first vaccination of Cohort 1 was done in July 2015 in Banfora, Burkina Faso.

Trial schedule



<BK-SE36/003 Trial>

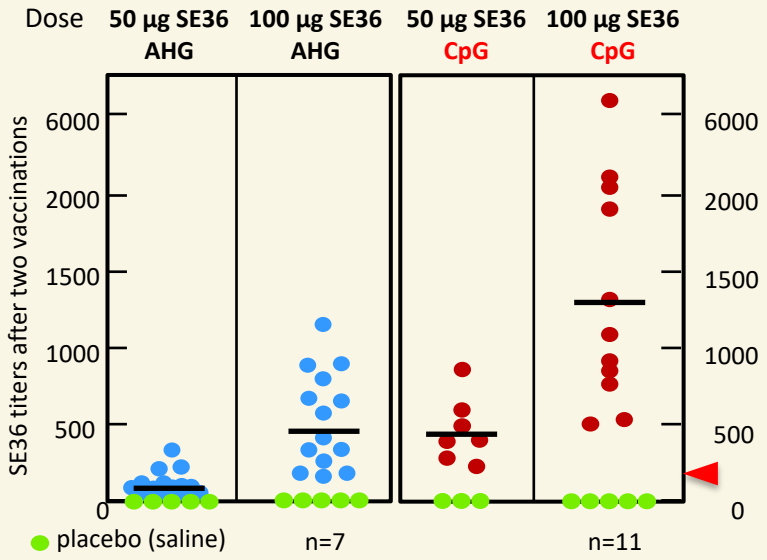
Clinical Trial (Phase Ia) of Malaria Vaccine Candidate NPC-SE36 /CpG, a Novel Formulation with CpG Oligonucleotide as Adjuvant



(The figure is prepared by Professor Horii)

Immunity to combat pathogens entails both innate immunity that responds immediately once a pathogen attacks, and acquired immunity that can be induced by infection or vaccination. Induction of both innate and acquired immunity (using an antigen from a pathogen) should result to a strong immune response.

CpG (K3) ODN is a novel adjuvant that activates innate immunity. The addition of the adjuvant to NPC-SE36 is expected to enhance the immune response. After pre-clinical testing of NPC-SE36 with CpG, Phase Ia clinical trial was conducted at Osaka University Medical Center for Translational and Clinical Research. The new formulation induced several times higher antibody titer compared to previous NPC-SE36 formulation.



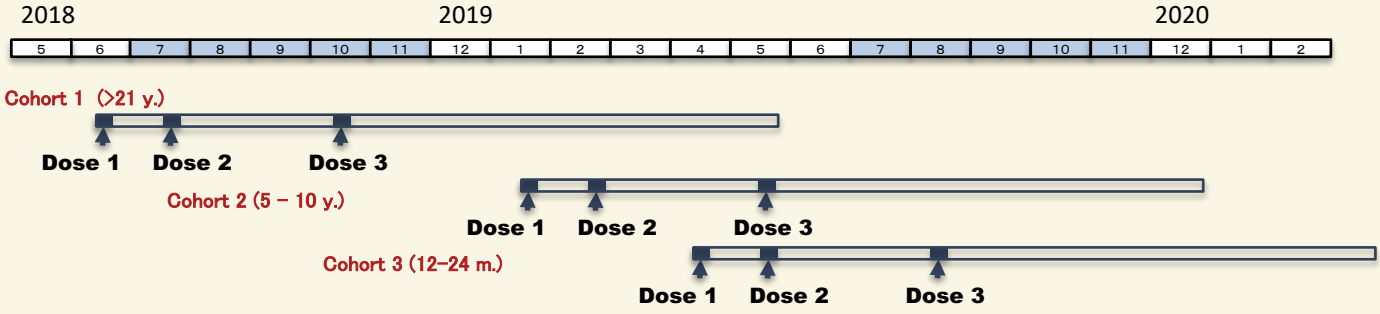
Horii et al., Parasitol Int. 2010; 59:380-6. *(Un-published), 2019*

The immunogenicity data was obtained from P1a trial with BK-SE36 and P1a trial with BK-SE36/CpG in Japan and these trials were conducted prior to conducting P1b trial with BK-SE36 and P1b trial with BK-SE36/CpG in Burkina Faso.

Clinical Trial (Phase Ib) of Malaria Vaccine Candidate NPC-SE36/CpG from Adults to 1-year-old Children in Burkina Faso

NPC-SE36/CpG was reasonably well tolerated in Japanese adult volunteers with no history of malaria infection. Clinical trial in Burkina Faso is ongoing (April 2019 - present). We are now vaccinating cohort 3 (12-24 month-old children) after safety assessments were done and confirmed in adults (>21 years-old) and children 5-10 years old (cohort 2). The vaccine group is made up of 30 volunteers, with 15 volunteers for the placebo group.

Trial schedule



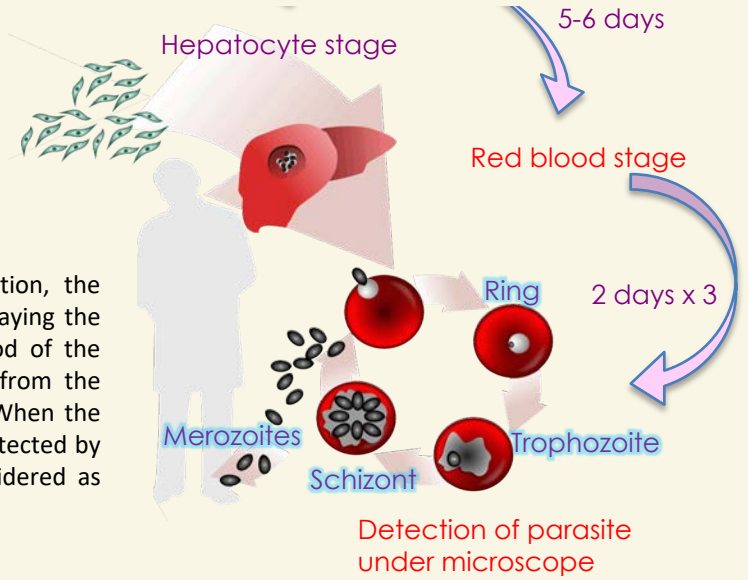
So far there are no reported serious adverse events related to vaccination.

<NPC-SE36/001 Trial>

Future Plans
Conduct of Controlled Human Malaria Infection (CHMI) Study

About CHMI:
CHMI is a tool/model that is increasingly being used to find the vaccine effect prior to large-scale clinical trials. Cultured *Plasmodium* sporozoites are introduced to volunteers' vein to reliably initiate infection and determine protective effect especially
in malaria naive volunteers.

GMP-produced malarial parasite at sporozoite stages are introduced via the subject's vein.



If vaccination is done prior to sporozoite inoculation, the growth inhibitory effect on sporozoite results in delaying the appearance of the parasites in the peripheral blood of the vaccinees. The inhibitory effect can be calculated from the delayed days in the parasite appearance in blood. When the inhibitory effect exceeds 90%, parasite cannot be detected by blood microscopy examination, and it can be considered as protected.

Palacpac et al. Vaccine 29 (2011) 5837–5845

Development Partners

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Toshihiro Horii Bio:
Born in Osaka in 1953. Graduated from the Department of Biology, Faculty of Science, Osaka University, 1976. Associate Professor in the Research Institute for Microbial Diseases (RIMD), Osaka University in 1991 and as Professor in 1999. He served as Director for two special research facilities under RIMD: Research Center for Infectious Disease Control and International Research Center for Infectious Diseases. After his retirement in 2019, he became Professor in the Donated Research Division for Malaria Vaccine Development.