Clinical Development of Malaria Vaccine BK-SE36

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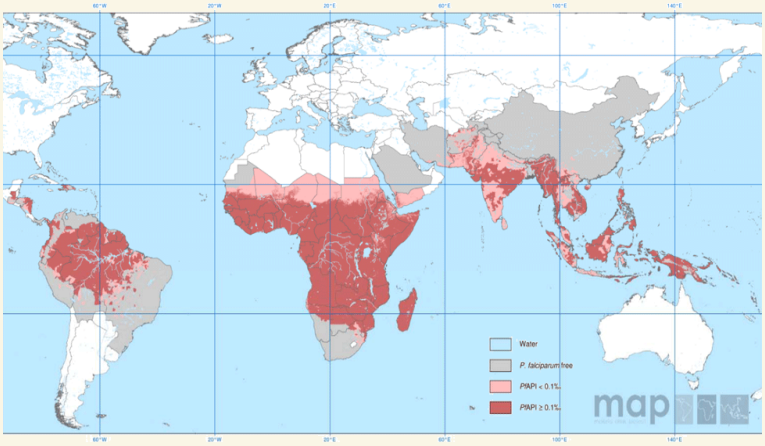
Malaria

Malaria, a tropical disease transmitted by anopheles mosquito, causes over two hundred million clinical illness and 438,000 deaths annually. Majority of the burden is in children under 5 years in sub-Saharan African countries. Pregnant women in the same region also suffer from pregnancy malaria. This disease is a serious obstacle for economic development as well as health.

Mothers holding babies with severe malaria



Malaria endemic regions

Global death due to malaria

Increased with the spread of chloroquine resistant parasites (1980-2005) and decrease by introduction of Coartem (2005-2010)

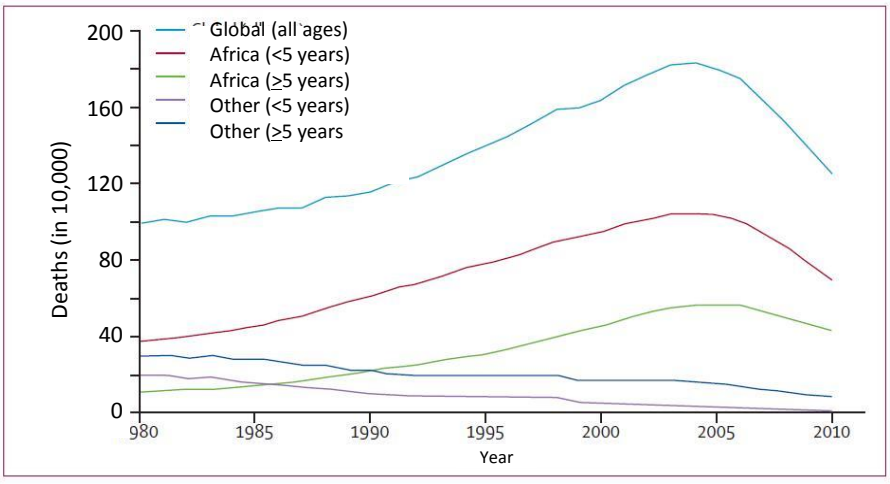


Figure 2: Trends in global malaria deaths by age and geographical region, 1980 to 2010

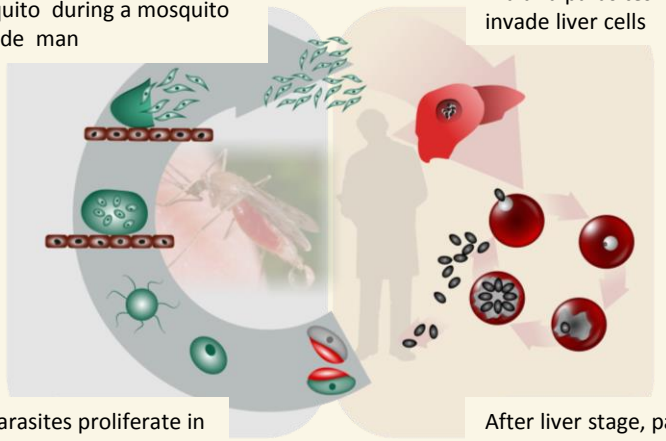
Children from a village in Burkina Faso, Africa

Rationales for malaria vaccine development

- ✔☐ Serious obstacle for health and economic growth in sub-Saharan African countries.
- ✔☐ Protection for people who are dispatched to malaria endemic areas (businessmen, those in humanitarian aid, embassy staff, national armed forces)
- ✔☐ Protection for migrant workers to Africa, for example Chinese and Indian workforce

Malaria parasites leave salivary gland of the mosquito during a mosquito bite to invade man

Malaria parasites first invade liver cells



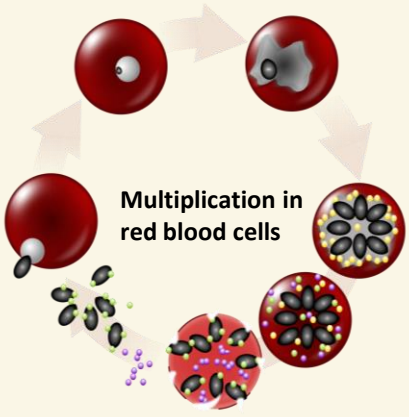
Malaria parasites proliferate in the mosquito, ready for the next infection.

After liver stage, parasites penetrate into the red blood cells and grow exponentially.

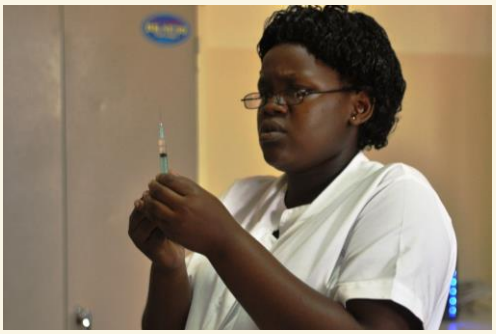
Blood-sucking Anopheles mosquito

BK-SE36 malaria vaccine

BK-SE36 malaria vaccine is a freeze-dried formulation of recombinant SE36 protein that was expressed in *E. coli* and adsorbed to aluminum hydroxide gel. The vaccine formulation is stable for half of year under room temperature. SE36 protein is derived from SERA antigen gene of the malaria parasite, *Plasmodium falciparum.* SERA is essential for parasite growth and is expressed in the red blood cell stage. SERA antigen functions during parasite egress and red blood cell invasion. The SE36 protein induces antibodies that inhibits growth of the parasite.



Clinical trial of the BK-SE36 malaria vaccine in Uganda and follow-up research



Approved by Ugandan government authorities, the trial was conducted in compliance with the International Conference on Harmonization Good Clinical Practices and regulatory requirements from 2010 to 2011. After safety assessment in men and women above 21 years old, vaccination in 6-20 years old was carried out. Health and presence of blood stage parasites were further monitored in a follow-up research for over one year for 6-20 year olds.

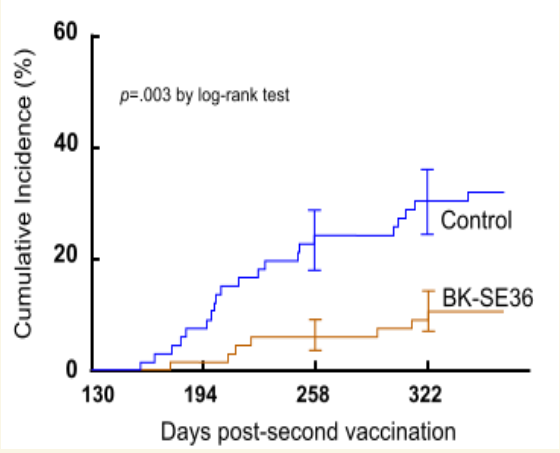
Number of subjects

Cohort1	BK-SE36 vaccine 1.0 mL		Control vaccine 1.0 mL	
	male	female	male	female
Sero negative to SE36	9	9	5	5
Sero positive to SE36	9	9	5	5

Cohort 2	BK-SE36 vaccine		Control vaccine	
	0.5 mL	1.0 mL	0.5 mL	1.0 mL
6-10 y.	11	11	3	3
11-15 y.	11	11	3	3
16-20 y.	11	11	3	3

BK-SE36 malaria vaccine

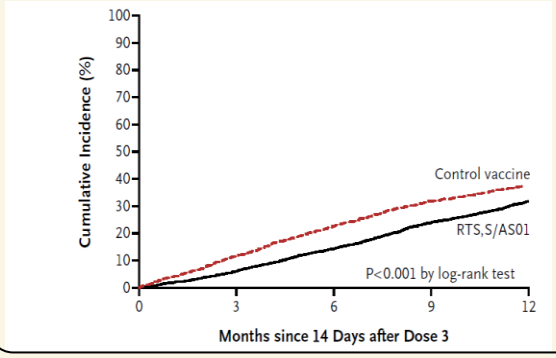
Follow-up research was carried out for BK-SE36 vaccinees (66 people) and control people without vaccination (66 people) for over 1 year. It was observed that the cumulative number of symptomatic malaria incidence in the vaccine group was less than that in the control group with protective efficacy of 72% (p=0.003). (PLOS ONE, 2013)

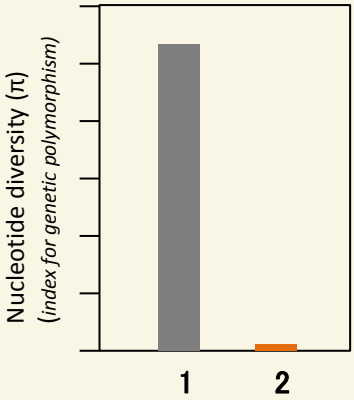


Comparison with other malaria vaccines

RTS, S/AS01A vaccine is developed by GSK (Glaxo Smith Kline)

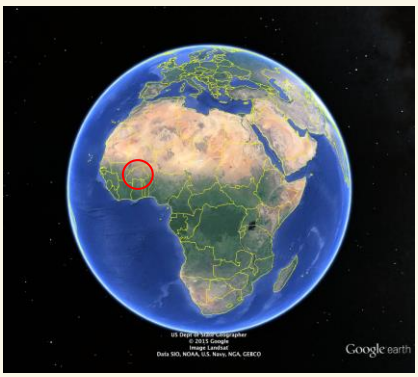
After three vaccinations, protective efficacy in one year was 31.3% (NEJM, 2012). Approval is pending.





Analysis of genetic polymorphism of a large number of malaria parasites collected in Tanzania. Column 1 shows high diversity of the gene on which RTS,S vaccine is based; column 2 shows a much lesser diversity of the gene on which SE36 is based. This is thought to be one of the major causes for differences in vaccine efficacy.

Proceeding to the BK-SE36 clinical trial for 1-5-year-old children in Burkina Faso



The first vaccination of cohort 1 was carried out in July, 2015 at Banfora, Burkina Faso. After safety evaluation, the first vaccination of cohort 2 was carried out in October 2015.

Number of subjects

Cohort	*Vaccine*	*Route of vaccination*	*number*
1: 25-60 month old children	1. BK-SE 36	subcutaneous	18
	2. BK-SE 36	intra-muscular	18
	3. Control vaccine	intra-muscular	18
2: 12-24 month old toddlers	1. BK-SE 36	subcutaneous	18
	2. BK-SE 36	intra-muscular	18
	3. Control vaccine	intra-muscular	18
			108

Osaka University is collaborating with European Vaccine Initiative (Heidelberg) and Burkina Faso National Malaria Research and Training Center for Phase Ib clinical trial of BK-SE36 (1-5-year-olds, 2015-2017). This trial is supported by GHIT Fund and Nobelpharma Co.

GHIT Fund
Global Health Innovative Technology Fund

Nobelpharma

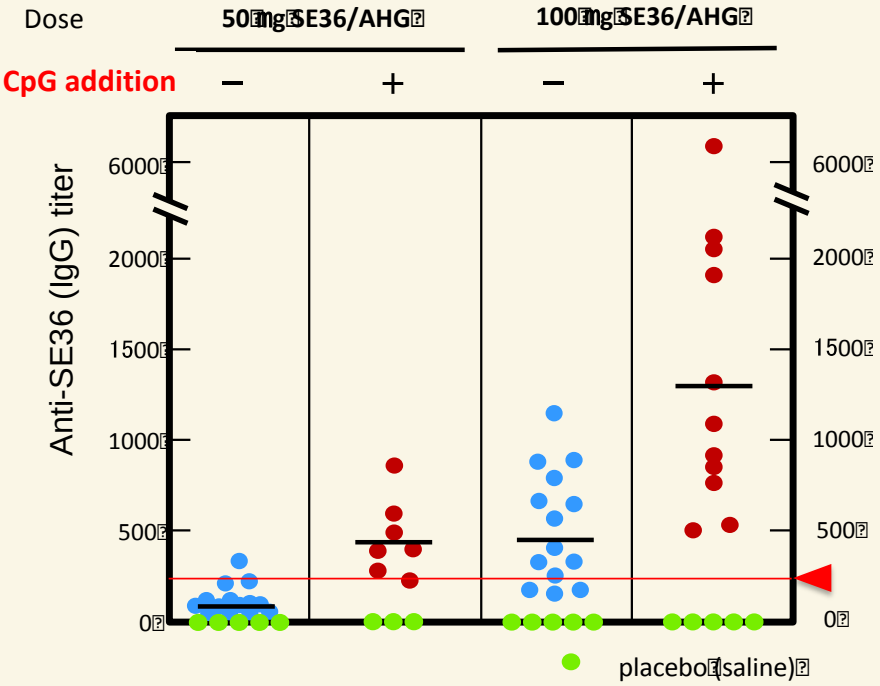
BK-SE36/CpG, a novel formulation with CpG oligonucleotide as adjuvant

CpG (K3) ODN (ATCGACTCTCGAGCGTTCTC) is a novel adjuvant that is expected to have strong immune enhancing effect.

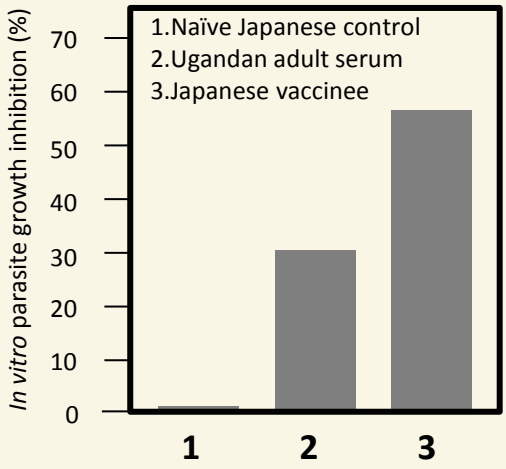
Number of subjects

	Vaccine group	Dose	SE36 amount per dose	Al amount per dose	CpG amount per dose	No of vaccinees
Cohort 1	BK-SE36/CpG	0.5 mL	0.05 mg	0.5 mg	0.5 mg	7
	Control		0.0 mg	0.0 mg	0.0 mg	3
Cohort 2	BK-SE36/CpG	1.0 mL	0.1 mg	1.0 mg	1.0 mg	11
	Control		0.0 mg	0.0 mg	0.0 mg	5

Higher antibody titer was induced by addition of CpG adjuvant.



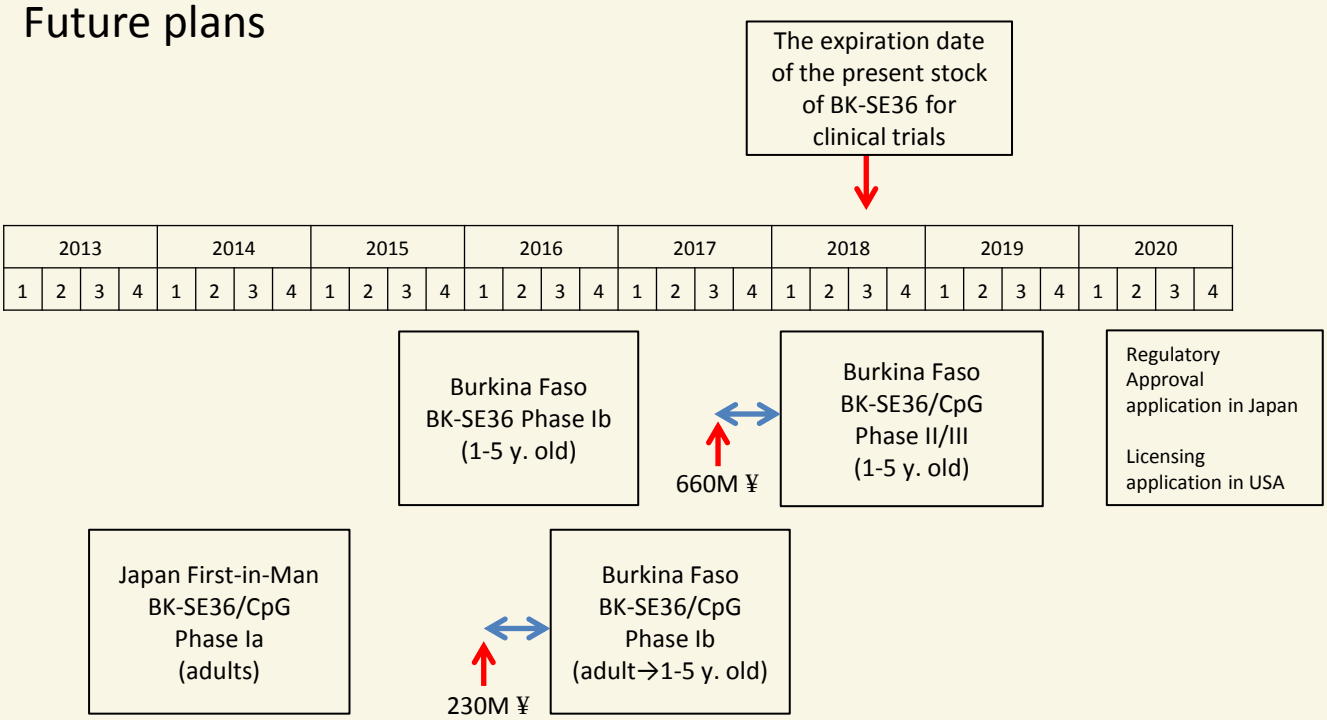
Sterile immunity could be obtained for 1 year when the vaccine induced antibody titer is over this threshold.



After a 24 hour assay, *in vitro* parasite growth inhibition activity was obtained with serum collected from BK-SE36/CpG vaccinee and pooled Ugandan adult serum.

BK-SE36/CpG vaccination induced parasite growth inhibitory antibodies. The inhibition observed was greater than that observed for people who have experienced infections for many years in malaria endemic areas.

Future plans



↑ Required Funds

↔ 6 months prior to start of clinical trial, ethics approval and regulatory requirements have to be applied for in Burkina Faso. At this time it is necessary to specify source of funds for trial conduct/activities.

After the expiration date of the current clinical batch of BK-SE36, it is necessary to build a new production line which needs an additional investment of about ¥2 billion.

-Conclusion-

We have shown that BK-SE36 malaria vaccine has a promising protective efficacy (72%) in the 6-20 year-old children and young adults in Uganda. Based on our analysis of the induced antibody response, even higher protective efficacy (80%) can be expected in children under 5-year-old, the WHO designated target population. In addition, even higher efficacy can be expected by the addition of CpG, especially for travelers to malaria endemic areas.

Organizations involved in the development

- **Research Institute for Microbial Diseases, Dept. of Mol. Protozoology** **Toshihiro Horii (Prof)**
  Basic research, Support for clinical trial, Monitoring
- **The Research Foundation for Microbial Diseases of Osaka University** **Koichi Yamanishi（President）**
  BK-SE36 GMP manufacturer, clinical trial design, implementation and supervision
- **Osaka City University School of Medicine and Public Health** **Yoshio Hirota（Prof. Emeritus）**
  Statistical analyses of data
- **Osaka University Medical Center for Translational Research** **Yoshiki Sawa（Dean, Med. Sch.）**
  First-in-Man investigator initiated clinical trial for BK-SE36/CpG
- **(Ltd) GeneDesign , Inc** **Kazuhiko Yuyama (President)**
  CpG GMP manufacturer
- **Uganda BK-SE36 Malaria Vaccine Working Group** **Tom Egwang (Head)**
  Conduct of clinical trial in Uganda
- **(Ltd) Nobelpharma Co.** **Jin Shiomura (President)**
  Clinical trial sponsor/partner
- **Centre National de Recherche et de Formation sur le Paludisme** **Sodiomon Sirima (Head)**
  Conduct of clinical trial in Burkina Faso
- **European Vaccine Initiative (EVI)** **Odile Leroy (Sec General)**
  Clinical Trial Coordination

TOSHIHIRO HORII

BIOGRAPHY

BIRTHYEAR: 1953
1976 B.A. Biology, Osaka University; 1980 Research Associate, Osaka University; 1984 Two years at Dartmouth Medical School, Hanover, NH for research on molecular genetics and start of malaria research; 1991 Assistant Professor, Research Institute for Microbial Diseases of Osaka University; 1999 Professor; 2005 Director, Research Center for Infections Disease Control and International Research Center for Infectious Diseases, Osaka University

Awards: 2004 The 51st Koizumi Prize, The Japanese Society of Parasitology
2004 The 50th Takeda Science Foundation Specific Research Grant
2014 Masamichi Aikawa Medal, Japanese Society of Tropical Medicine

Memberships:
The Japanese Society of Parasitology, President
The Japanese Society for Vaccinology, member of a board of trustees
The Japanese Society of Tropical Medicine
The Japanese Society of Molecular Biology

<u>Major Grants for BK-SE36 Malaria Vaccine Development</u>

Grant-in-Aid for Scientific Research on Priority Areas, MEXT（1996-1999, 2003～2007, 2008-2012）
Grant-in-Aid for Scientific Research (A), MEXT （1999-2000、2012-2015）
Grant for the Knowledge Cluster Initiative, MEXT （2002-2006、2007-2011）
Translational Research Promotion Project, NEDO (New Energy and Industrial Technology Development Organization) （2009-2011）
Cost for follow-up research of BK-SE36 clinical trial(phase Ib), The Research Foundation for Microbial Diseases of Osaka University （2011）
International Collaborative Research Program for Integrated Promotion of Social System Reform and Research （2011-2016）
Grant for Translational Research Network Program, MEXT （2012-2015）
GHIT Fund RFP Product Development Platform （2013-2015, 2014-2016）