BK-SE36 malaria vaccine candidate for young children

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SE36 protein is derived from P47 of SERA5. Serine repeats in P47 protein was removed because of its hydrophobic nature. Recombinant protein is produced in *E. coli* from a synthetic gene.

Horii et al., *Vaccine* (2010)
Correlation of anti–SE36 antibody levels with parasitemia in residents from the Solomon Islands

(Horii et al., 2010, Parasitol Int.)
Sero-positive rate against N-terminal domain of SERA is very low in younger generations and increases with age.

(Horii et al., 2010, Parasitol. Int.)
Function of SERA5

- Central domain, P50, is essential for schizont rupture, although mechanism is unclear.

- N-terminal and C-terminal domain binds to vitronectin for host immune modulation (unpublished data).

- N-terminal and C-terminal domain on merozoite has an essential function in RBC invasion (unpublished data).
Clinical trials of BK-SE36 in Uganda

BK-SE36:
GMP grade SE36 protein formulated with aluminum hydroxide gel

Phase Ib in Uganda:

Stage 1: malaria-”exposed” Ugandan adults (21-40 years old)
- No severe adverse events

2010 Apr – Aug

Stage 2: malaria-”exposed” Ugandan children and young adults (6-20 years old)
- No severe adverse events

2010 Sep – 2011 Feb

Stage 2: Follow-up

2011 Mar – Nov

Palacpac et al., PLoS ONE May 2013, Vol. 8
**Phase 1b: Trial design**

**Stage 1**
1 dose = 1.0mL

(=100µg SE36 protein with 1mg aluminum hydroxide gel)

**Stage 2**
2 dose = 0.5 and 1.0mL

<table>
<thead>
<tr>
<th>BK-SE36</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Sero-negative</td>
<td>9</td>
</tr>
<tr>
<td>Sero-positive</td>
<td>9</td>
</tr>
</tbody>
</table>

**Stage 1, 21-40 y: 56 subjects**
- 1 dose = 1.0mL

<table>
<thead>
<tr>
<th>BK-SE36</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>6-10 y old</td>
<td>11</td>
</tr>
<tr>
<td>11-15 y old</td>
<td>11</td>
</tr>
<tr>
<td>16-20 y old</td>
<td>11</td>
</tr>
</tbody>
</table>
### Administration site reactions

#### Stage 1, 21-40 y

<table>
<thead>
<tr>
<th></th>
<th>BK-SE36 (1.0mL)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sero-negative n=18</td>
<td>Sero-positive n=18</td>
<td></td>
</tr>
<tr>
<td>Induration</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Pain/Tenderness</td>
<td>13</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Edema/Swelling</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Erthema/Redness</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>(Other: Hyperpigmentation)</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

#### Stage 2, 6-20 y

<table>
<thead>
<tr>
<th></th>
<th>BK-SE36</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5mL n=33</td>
<td>1.0mL n=33</td>
<td></td>
</tr>
<tr>
<td>Induration</td>
<td>31</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Pain/Tenderness</td>
<td>19</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Edema/Swelling</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Erthema/Redness</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>(Other: Hyperemia/Hyperpigmentation)</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Safety and administration site reactions were similar to Phase 1a trial of this vaccine.
Young children remarkably responded to BK-SE36.
Follow-up study

84 administered subjects

BK-SE36 (0.5 mL): n = 33
BK-SE36 (1.0 mL): n = 33
Placebo (0.5 mL): n = 9
Placebo (1.0 mL): n = 9

New subjects

Age, gender and locality matched
Control: n = 50

Monthly visits + Any time when sick

Serum sampling

• Active surveillance: monthly
• Passive surveillance: any time when a subject felt sick

→ Detection of malaria infection and parasitemia
Vaccine efficacy

Days to the first appearance of malaria parasites ≥5000/µL + 37.5°C in control and vaccine groups (0.5mL + 1.0 mL)

Protective efficacy against parasitemias ≥5000/µL + fever
BK-SE36= 72%, p=0.003

Palcpac et al., 2013 PLOS ONE
Definition of responders to BK-SE36

- Responder (n=20)
- Non-responder (n=44)
- Placebo (n=16)

Fold increase in antibody titer:
- BK-SE36
- Placebo
Responder to BK-SE36

Percentile of population with ≥2 fold increase in antibody titers according to age group of vaccine cohort

<table>
<thead>
<tr>
<th>Dose</th>
<th>6–10y.</th>
<th>11–15y.</th>
<th>16–20y.</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 μg</td>
<td>72.70%</td>
<td>27.30%</td>
<td>18.20%</td>
</tr>
<tr>
<td>50 μg</td>
<td>36.40%</td>
<td>0%</td>
<td>27.30%</td>
</tr>
</tbody>
</table>
Analysis of boosting effect by natural infection

- Vaccine response
  - Fold increase
  - $\geq 1.92$ : Responder
  - $< 1.92$ : Non-responder

Infection: $\geq 100$ parasites / $\mu l$ blood

i) Infection was found between monthly visits.

ii) Infection was found at a monthly visit.

Before | After
---|---
Titer increase

Before | After | Next visit
---|---|---
Titer increase
Boosting effect after natural infection

- **Responder**: Significant increase in antibody titer after natural infection, with a geometric mean of fold increase significantly higher in responders compared to non-responders or placebo/control groups.

- **Non-responder**:较小的抗体滴度变化，但与对照组或非响应者相比无显著差异。

- **Placebo/Control**: 显著降低，但与非响应者和对照组相比变化不大。

Statistical analysis:
- **Responder vs. Non-responder**: $P<0.001^{***}$
- **Non-responder vs. Placebo/Control**: $P=0.002^{**}$
- **Placebo/Control vs. Non-responder**: $P=0.42$
Subjects in the responder group without infection have higher antibody titers at initial (21 days post vaccination). The antibody titers of subjects with infection were significantly boosted by natural infection.
Correlation between vaccine response and re-infection

Parasitemia $\geq 100$ (detection limit)

<table>
<thead>
<tr>
<th>No. of infections</th>
<th>0</th>
<th>1</th>
<th>$\geq 2$</th>
<th>Risk of $\geq 2$ infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>9</td>
<td>9</td>
<td>2</td>
<td>$0.100$ $(2/20)$</td>
</tr>
<tr>
<td>Non-responder</td>
<td>18</td>
<td>16</td>
<td>12</td>
<td>$0.261$ $(12/46)$</td>
</tr>
<tr>
<td>Placebo/Control</td>
<td>25</td>
<td>19</td>
<td>22</td>
<td>$0.333$ $(22/66)$</td>
</tr>
</tbody>
</table>

(by Fisher’s exact test)
The nucleotide diversities ($\pi$) of SE36 are lower than those of *ama 1*, *msp1* and *csp* genes.
Phase 1a trial (2005)  malaria-naïve Japanese adults

Group 1: 50 µg SE36 (0.5mL)
Group 2: 100 µg SE36 (1.0mL)

Anti-SE36 (IgG) titer

After 1st administration  After 2nd administration  After 3rd administration

After 1st administration  After 2nd administration  After 3rd administration

Horii et al., Parasitol Int. 2010

, placebo (saline)
Phase Ib trial in Uganda; The highest response was observed in the youngest cohort.

Younger age group of 0-5 years old would be more responsive to BK-SE36 vaccination

Follow-up study revealed the efficacy of BK-SE36 against several malaria endpoints

Vaccine responders had lower risk of re-infection and did show boosting effects by natural infection
The European Vaccine Initiative (EVI) is leading European efforts to develop effective, accessible, and affordable vaccines against diseases of poverty. EVI's vision is 'a world free of the intolerable burden of diseases of poverty within the coming decades'.

EVI is contributing to the global efforts to control these diseases in three main ways:

- Creating an environment to accelerate the development and clinical assessment of vaccine candidates for diseases of poverty
- Promoting affordability and accessibility of vaccines for diseases of poverty in low-income populations
- Seeking to align all major stakeholders and acting as a focal point to ensure the successful development of vaccines for diseases of poverty for low-income populations.

The Centre National de Recherche et de Formation sur le Paludisme (CNRFP) was founded to guide the development and implementation of the Burkina Faso national malaria control programme, including research to identify new malaria control measures and adapt existing ones to local conditions. It is an important site for genetic epidemiology of malaria because of the hyper-endemic malaria in a variety of populations with different genetic backgrounds. CNRFP works closely with the University of Rome 'La Sapienza'.

**People**

- Sodionmon Sirima (MalariaGEN Investigator)
- Edith Bogauma (MalariaGEN Research Coordinator)

**Sodionmon Sirima**

Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Ouagadougou, Burkina Faso

Dr Sodionmon Sirima has been Head of the Research and Training Department of the Centre National de Recherche et de Formation sur le Paludisme (CNRFP) since 1995. He is also Head of the Malaria Vaccine Development program in Burkina Faso.

Dr Sirima holds a PhD in Epidemiology from the University of Rome, "La Sapienza", Italy in addition to a medical degree (MD) and a Masters in Social Anthropology from the University of Ouagadougou, Burkina Faso. He has been working on the genetic epidemiology of Plasmodium falciparum malaria, including the mechanisms by which the parasite causes the disease and the clinical features of severe malaria. Sodionmon Sirima and his team are contributing to Consortial Project 1, Consortial Project 2 and Consortial Project 3.
Double blinded randomized Phase Ib clinical trial of BK-SE36 in Burkina Faso

Cohort 1
(25 - 60 months)

Dose 1  Dose 2  Booster Dose

Cohort 2
(12 - 24 months)

Dose 1  Dose 2  Booster Dose

Treatment arms in each cohort
18 Vaccinees by intra-muscular
18 Vaccinees by subcutaneous
18 Placebo vaccinees (Synflorix)

Endpoints
Safety in young child
Immunogenicity
Exploratory efficacy
Development of *Next Generation* SE36 Malaria Vaccine
For having a stronger immunogenicity.

Formulation with innate immune adjuvant,
CpG K3 ODN  (TLR9 ligand adjuvant)
Comparison of vaccine induced antibody titers after 3 weeks of the second administration between BK–SE36 and BK–SE36/CpG in Phase Ia clinical trials of Japanese naïve adult (male)
Comparison of subclass, epitopes, protective ability and etc. of the induced IgG
Acknowledgement

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Yoshio Hirota, Wakaba Fukushima, Kazuya Ito

BK-SE36 Malaria Vaccine Working Group- MBL and LMC, Uganda:

Medical Center for Translational Research, Osaka University Hospital
Akira Myoui, Sachiko Ezoe,

Masanori Yagi Nirianne Palacpac
## Immunogenicity of BK-SE36

**Phase 1b trial:** malaria-”exposed” Ugandan adults  
**Stage 1, 21-40 yr.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Sero-conversion</th>
<th>Administration</th>
<th>No. of subjects</th>
<th>Before 1st administration</th>
<th>3 weeks after 2nd administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Negative</td>
<td>BK-SE36</td>
<td>9</td>
<td>22.0 (12.1-40.2)</td>
<td>34.5 (21.7-54.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>5</td>
<td>36.8 (8.8-154.7)</td>
<td>26.3 (4.5-155.3)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>BK-SE36</td>
<td>9</td>
<td>469.3 (260.8-844.5)</td>
<td>496.7 (254.7-968.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>5</td>
<td>495.7 (114.0-2155.5)</td>
<td>340.4 (67.7-1713.1)</td>
</tr>
<tr>
<td>Male</td>
<td>Negative</td>
<td>BK-SE36</td>
<td>9</td>
<td>35.9 (22.7-56.7)</td>
<td>59.1 (44.8-77.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>5</td>
<td>24.4 (13.7-43.4)</td>
<td>29.8 (9.0-98.6)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>BK-SE36</td>
<td>9</td>
<td>465.4 (207.7-1042.9)</td>
<td>403.9 (205.7-792.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>5</td>
<td>237.5 (142.8-395.2)</td>
<td>333.1 (145.9-760.4)</td>
</tr>
</tbody>
</table>

*In healthy adults, largest increase in mean anti-SE36 protein antibody were observed in subjects with low baseline antibody titers to SE36.*

Palacpac et al., *PLoS ONE* May 2013, Vol. 8
# Immunogenicity of BK-SE36

**Phase 1b trial:** malaria-"exposed" Ugandan children and young adults  
**Stage 2, 6-20 yr.**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Administration</th>
<th>No. of subjects</th>
<th>Before 1st administration</th>
<th>3 weeks after 2nd administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-10 y old</td>
<td>BK-SE36 1.0 mL</td>
<td>11</td>
<td>25.3 (9.0-71.1)</td>
<td>124.7 (46.8-332.6)</td>
</tr>
<tr>
<td></td>
<td>BK-SE36 0.5 mL</td>
<td>11</td>
<td>26.0 (12.8-52.6)</td>
<td>48.0 (27.4-84.3)</td>
</tr>
<tr>
<td>11-15 y old</td>
<td>BK-SE36 1.0 mL</td>
<td>11</td>
<td>81.9 (35.3-189.9)</td>
<td>100.6 (42.0-240.6)</td>
</tr>
<tr>
<td></td>
<td>BK-SE36 0.5 mL</td>
<td>11</td>
<td>77.5 (42.1-142.6)</td>
<td>63.5 (36.6-110.2)</td>
</tr>
<tr>
<td>16-20 y old</td>
<td>BK-SE36 1.0 mL</td>
<td>11</td>
<td>167.8 (60.1-468.5)</td>
<td>204.9 (79.0-531.4)</td>
</tr>
<tr>
<td></td>
<td>BK-SE36 0.5 mL</td>
<td>11</td>
<td>133.5 (44.7-398.5)</td>
<td>156.2 (56.6-431.0)</td>
</tr>
<tr>
<td>6-20 y old</td>
<td>Placebo</td>
<td>18</td>
<td>80.8 (40.6-160.7)</td>
<td>53.8 (30.2-94.9)</td>
</tr>
</tbody>
</table>

Antibody titer is relative to 5,000 units assingd for high titer pooled Ugandan serum  
Palacpac et al., *PLoS ONE* May 2013, Vol. 8