Reduced antibody responses against *Plasmodium falciparum* vaccine candidate antigens in the presence of *Trichuris trichiura*
Malaria: about 70% of the cases and 90% deaths (in Africa)

Helminthic infections: ± 1 million deaths per year and cause malnutrition, anemia, stunted growth…. (mainly in Africa)
Progress on Malaria Vaccine Research

- Control effort has decreased the mortality,
- Parasites and anopheles develop resistance =>
- Malaria vaccine: great contribution to control/eliminate malaria

GMZ2 Malaria Candidate Vaccine

• Blood stage candidate vaccine

• *Plasmodium falciparum* fusion protein composed of:
  - Glutamate-Rich Protein (GLURP) AA 27–500 and
  - Merozoite Surface Protein 3 (MSP3) AA 212–318

• Expressed in *Lactococcus lactis*
Clinical Development of GMZ2

Phase 1a
Malaria-naive Germans

GMZ2 was safe, well tolerated and immunogenic

Phase 1b
Malaria-exposed Gabonese adults

Malaria-exposed children
(1 - 5 years old)

GMZ2 showed good safety and immunogenicity

Malaria-exposed children
(1 - 5 years old)

Multicenter trial at four African research institutions (Phase IIb)
Rationale for this study

- High prevalence of helminth infections in young African children
- Intestinal helminths modulate the host’s immune system; likely to reduce vaccine-induced immunity (TB, Influenza)
- In endemic populations removal of helminths can increase immune-reactivity (e.g. to environmental antigens)
Immune response during Malaria and Helminths infections

Blood stages of malaria parasites drive a Th1 immune response

Th1 immune response is down-regulated Helminths drive the immune response towards a Th2 and Treg response
Objective

Assess the influence of helminth infection on immune responses induced by GMZ2 vaccine candidate in Gabonese children during phase 1b trial
Study design and population

- Randomised, controlled, double-blind clinical trial
- Population: Healthy children aged 1 to 5 years (n = 30)
- Interventions:
  - \(30\mu g\) GMZ2 (n=10)
  - \(100\mu g\) GMZ2 (n=10)
  - Rabies (n=10)
- Single centre - Albert Schweitzer Hospital, Lambaréné, Gabon
- Trial Period: 09/2008 to 12/2009
Collection of stool and blood samples

- A plastic container distributed to all participants (D0 and D84)
  - Labeled with identification number
  - Container was returned with a portion of fresh morning stools

- Thick blood smear and blood sampling:
  - Systematically done at D0, D28, D56, D84 and D365,
  - In case of fever or history of fever
Analysis of blood and stool samples

<table>
<thead>
<tr>
<th>Test Description</th>
<th>D0</th>
<th>D28</th>
<th>D56</th>
<th>D84</th>
<th>D365</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA (IgG and sub-classes anti-GMZ2, anti-MSP3 and anti-GLURP)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>ELISPOT</td>
<td>x</td>
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<td>Kato Katz and Coproculture</td>
<td>x</td>
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</tbody>
</table>
Characterization of study population

10 female and 10 male received the GMZ2 (N=20)

Table 1. Baseline characteristics of study participants.

<table>
<thead>
<tr>
<th></th>
<th>Rabies</th>
<th>GMZ2-30</th>
<th>GMZ2-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) *</td>
<td>3.5 (1.9, 4.8)</td>
<td>3.5 (2.2, 5.6)</td>
<td>3.5 (1.8, 5.7)</td>
</tr>
<tr>
<td>Gender #</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>Height (cm) *</td>
<td>96 (85, 105)</td>
<td>94 (82, 114)</td>
<td>92 (77, 109)</td>
</tr>
<tr>
<td>Weight (kg) *</td>
<td>14.6 (11.4, 18.6)</td>
<td>13.7 (11.0, 21.8)</td>
<td>13.3 (9.6, 17.0)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl) *</td>
<td>10.3 (9.3, 11.9)</td>
<td>10.5 (8.6, 11.8)</td>
<td>10.5 (8.7, 11.8)</td>
</tr>
<tr>
<td>White blood cells (cells/ml) *</td>
<td>10.9 (8.3, 13.6)</td>
<td>9.6 (7.3, 13.4)</td>
<td>8.6 (6.1, 11.4)</td>
</tr>
<tr>
<td>Thrombocytes (cells/ml) *</td>
<td>387 (262, 487)</td>
<td>322 (222, 408)</td>
<td>381 (201, 516)</td>
</tr>
</tbody>
</table>

*mean (min, max), # female/male.
doi:10.1371/journal.pone.0022525.t001

Fig. 1: Helminth infection status (any species)
Helminths and antibodies (total IgG) responses against GMZ2 and its components

Fig. 2. GMZ2 and GLURP specific antibodies are lower in children infected with T. trichiura

Effects on IgG subclasses and memory B cells

- Estimation of the effect of hookworms on vaccine immune response: not possible with only one infection by hookworm.

- GMZ2-specific IgG-subclasses: similar in helminth positive and negative one month after the last vaccination.

- Memory B-cell responses: trend towards higher responses in *T. trichiura* negative children.
Conclusion

- Significantly lower GMZ2 and GLURP-Abs concentration in the presence of *T. trichiura*. To be confirmed in a prospective study.

- It is not clear how *T. trichiura* can modulate Ab production against vaccine antigens.

- Phase IIb multicenter trial shall provide further insights on the effects of parasites on vaccine efficacy.