Recombinant full-length *Plasmodium falciparum* circumsporozoite protein-based vaccine expressed in *Pseudomonas fluorescens* and adjuvanted with GLA-LSQ: results of Phase 1 testing with malaria challenge

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Introduction

The *Plasmodium falciparum* circumsporozoite protein (CSP) is an effective antigen for malaria vaccination. Monoclonal antibodies targeting the junction between the CSP N-terminus and central repeat region provided sterilizing protection in recent clinical trials.¹,² Full length recombinant CSP (rCSP) vaccines may offer advantage over CSP-based vaccines that do not include the junctional region, including RTS,S and R21.

The central repeat region makes a full-length CSP difficult to produce with good manufacturing practice, but new platforms have been able to overcome this hurdle, one of which expresses a recombinant CSP in a *Pseudomonas fluorescens* platform. CSP on its own is not highly immunogenic until a person has had repeated exposures,³ so CSP vaccines are generally combined with an adjuvant. Glucopyranosyl Lipid A-liposome *Quillaja saponaria* 21 formulation (GLA-LSQ) combines GLA, a synthetic, homogeneous, nontoxic derivative of Gram-negative bacterial cell wall lipopolysaccharide that functions as a TLR4 agonist, promoting Th1-type responses, and LSQ, a saponin extracted from a South American soapbark tree, which also promotes Th1-type responses and stimulates cytotoxic T cell production.⁴⁻⁵ Initial pre-clinical studies and first-in-human data showed promising immunogenicity of full-length rCSP vaccine given with GLA-LSQ (AP 10-602).⁶⁻⁷

Methods

We performed a Phase 1 clinical trial of a to investigate the safety, immunogenicity and efficacy against controlled human malaria infection (CHMI) of rCSP/GLA-LSQ (AP 10-602). Initial results demonstrated vaccine safety and immunogenicity.⁷ For the efficacy portion of the trial, 29 healthy, malaria-naïve Baltimore participants aged 18-45 years old were enrolled into three dosing arms: a high dose (60 µg rCSP + 5 µg GLA-LSQ), delayed 2 dose arm (n = 9), a high dose (60 µg rCSP + 5 µg GLA-LSQ), 3 dose arm (n = 10) and a low dose (10 µg rCSP + 5 µg GLA-LSQ), 3 dose arm (n = 10) given on days 1 and 490 (delayed 2 dose) or 1, 29, and 85 (3 dose) (Figure 1). The delayed high dose, 2-dose group was not initially part of the study design but resulted from COVID-related research shutdowns. Vaccinated participants and six unvaccinated infectivity controls underwent homologous CHMI 28 days after last vaccinations. Study endpoints included anti-CSP IgG antibody by ELISA and time to *P. falciparum* asexual parasitemia after CHMI.
Results

The high dose, 3-dose group achieved the highest geometric mean anti-rCSP IgG fold rise (day of CHMI/baseline): 236.2-fold, 95% CI: 32.4, 1721.1, compared to the low dose group: 55.4-fold, 95% CI: 8.3, 370.0, and the high dose, delayed 2-dose group: 33.3-fold, 95% CI: 1.3, 885.1 (Figure 2).
All vaccinated participants developed *P. falciparum* asexual parasitemia following CHMI (vaccine efficacy: 0%). Median time to parasitemia was eight days after CHMI in all groups and unvaccinated controls (Figure 3).

**Figure 3:** Kaplan-Meier Curves of Time to Malaria Infection after CHMI

Median peak parasite density (parasites per mL) was 58.05 (IQR: 35.65, 224.1) in the high dose, 3 dose group; 147.40 (IQR: 79.9, 409.30) in the high dose, delayed 2 dose group, and 102.80 (IQR: 54.0, 387.20) in the low dose, 3 dose group, and 296.25 (IQR: 129.20, 663.10) in the infectivity controls (Figure 4).
Discussion/Conclusions

While we saw a dose response relationship between the vaccine dose and IgG levels, the vaccine lacked efficacy. The lack of vaccine efficacy suggests that the vaccine construct and schedules given did not induce functional antibodies that reduce parasitemia or provide sterile protection. Potential explanations include antigen issues such as targeting of immunodominant versus protective epitopes or incorrect folding/presentation of epitopes, adjuvant issues such as suboptimal dose versus targeting the incorrect immune system pathways, or schedule issues such as need for a delayed 3rd dose versus a fractional 3rd dose. It is hoped that dissecting the immune responses to this vaccine will help to define protective responses for future vaccines.

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