Reviewer's report

Title: Limited antigenic diversity of Plasmodium falciparum apical membrane antigen 1 supports the development of effective multi-allele vaccines

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Reviewer: Clemens Kocken

Reviewer's report:

In this manuscript the authors describe the antigenic diversity of a major malaria blood stage vaccine candidate AMA1, based on antigen reactivity to human antibodies. They come to the conclusion that based on cross-reactivity, a careful selection of 3 allelic variants may be sufficient to cover antigen polymorphism in a vaccine. The data are new and interesting as previous analyses only took sequence polymorphism into account and not antigenic diversity.

The study is well designed and executed and a major issue of whether pooled sera can be used for such studies was well addressed and explained. In addition, a novel competition ELISA has been used. The discussion is somewhat long but interesting. There are only some minor issues to take into account to possibly improve the manuscript, detailed below.

Minor essential revisions.

1) Typo’s: Page 12, 2nd paragraph, littel should be little; Page 17, last line of 1st paragraph should read evaluation of antigenic diversity.... Page 19, last line 1st paragraph should read needs to be formally assessed;

2) Page 15, first paragraph, the authors state that antigenic diversity has been assessed by immunization of rabbits, that may have different responses than humans. There is at least one report (Kusi et al., 2011) that assesses antigenic diversity of AMA1 in rhesus monkeys that may, due to their close proximity to humans, far better mimic human responses than rabbits. The authors should take this into consideration as well.

3) Overall throughout the text when data are reported, the authors conclude firmly that based on their antigenicity studies the conclusion is that 3 AMA1 alleles, carefully selected, would be sufficient to cover polymorphism in a vaccine. Here they are confusing antigenicity and immunogenicity and only in the last line of the discussion they make a statement that is correct to this aspect. It would be more clear if the conclusions earlier in the manuscript are made a bit more cautious, making clear that the vaccine approach needs further evaluation and that this is merely a tool to make an educated guess of which alleles to combine in a vaccine.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I hold a patent on the DiCo approach for AMA1 vaccine development (Publication number US8741305 B2)