GENOME WATCH

How elusive can a malaria vaccine be?

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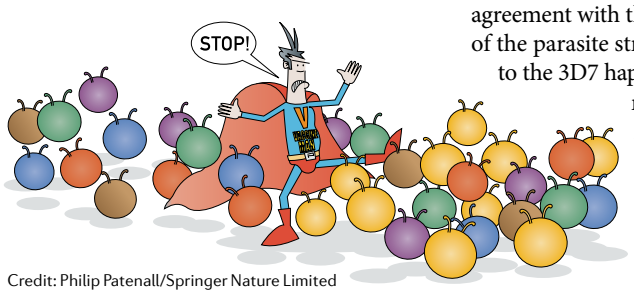
This month's Genome Watch explores the genetic variability of the anti-malaria vaccine protein and discusses its significance for an efficacious intervention.

Decades of research and intervention strategies have been devoted to attempts to control malaria around the world. Although these efforts have achieved varying degrees of success, the development of an efficient vaccine is sorely needed particularly in highly endemic areas. After decades of effort, a vaccine for malaria was licensed in 2015. The RTS,S/AS01 vaccine, which was developed by GlaxoSmithKline, consists of a recombinant protein containing a region of the *Plasmodium falciparum* circumsporozoite antigen that is fused with hepatitis B surface protein and reconstituted with a novel adjuvant AS01. The circumsporozoite protein is a major surface component of the sporozoite, which is the stage of the parasite that is injected into humans by infected female mosquitoes and invades liver cells to initiate the infection. The circumsporozoite antigen has three domains: a conserved amino-terminal region; a central region containing 37–44 NANP amino acid repeat sequences, which forms the immune-dominant B cell epitope; and a polymorphic carboxy-terminal region that elicits a T cell response. The peptide used in the vaccine includes 19 NANP repeats and the C-terminal region of the circumsporozoite protein from the widely used laboratory strain 3D7. This clone is derived from the NF54 strain, which was isolated from a patient in the Netherlands and, based on its genomic sequence, is of African origin.



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After a series of trials demonstrating efficacy of the RTS,S/AS01 vaccine against infection as well as clinical disease in various countries, a three-dose phase III trial was conducted between 2009 and 2014 involving 15,500 children across 11 sites throughout seven countries in Africa. The results showed a reduction in clinical malaria in children of 28% that increased to 36.3% with a booster provided 18 months after the third dose[1].

The gene encoding the circumsporozoite protein (*Pfcsp*) harbours great genetic diversity, and several studies have addressed the question of whether the variation in the efficacy of the vaccine is due to allele specificity. The most advanced sequencing technology (Illumina MiSeq and PacBio) was used for the analysis of almost 7,000 vaccinated and non-vaccinated children and revealed a reduction of vaccine efficacy from 50% for parasites with a perfect match to the vaccine circumsporozoite protein to 33% for those presenting any amino acid differences in this region[2]. Interestingly, the 50% efficacy of the vaccine found with matching parasites hints at the involvement of additional factors influencing the human immune response to the parasite. A recent study corroborated these findings with a small-scale sample population across two African countries and extended the analysis to include sequences from the Pf3K database, which contains samples from Africa and Asia[3]. This study found 393 unique *Pfcsp* haplotypes, of which 7 account for 51.3% of the total 4,000 samples. In agreement with the previous work, only 5.3% of the parasite strains sequenced correspond to the 3D7 haplotype across Africa and the match is much lower (0.25%) in Asian samples. These studies also detected the presence of the 3D7 haplotype in the context of multi-clonal infections, often representing a minority contribution to the parasite population. Another smaller scale but more global work, including samples from Asia, Oceania, South America and Africa, reported a global frequency of the full *Pfcsp* 3D7 haplotype of 1.71%, observed mainly in Africa[4]. However, the N-terminal region of the protein, also included in this analysis, showed much lower diversity across continents.

The high genetic diversity observed in the circumsporozoite protein and the low prevalence of the vaccine haplotype suggest that allele-specific immunity is important for the response elicited by the vaccine and could explain some of the efficacy variation observed in the phase III trials, pointing to a more challenging applicability worldwide. Both studies[3,4] showed little inter-continental overlap of haplotypes, which together with the high incidence of multi-clonal infections strongly argues in favour of a combination of main regional haplotypes in an improved version of the vaccine or the development of individual vaccines for different geographical regions. The lower diversity in the N-terminal region of the protein, which is functionally important and has a role in immunity, makes the inclusion of this region in an improved version of the vaccine an attractive possibility.

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Competing interests
The author declares no competing interests.