

## Q1. Which antigen on the infected erythrocyte surface is the target for acquired immunity to falciparum malaria?

**Too easy – it's PfEMP1 (*Plasmodium falciparum* erythrocyte membrane protein 1)** – ½ mark for correct answer, ½ mark for spelling out the acronym, subtract ½ mark for being cheeky!

Whilst a commonly accepted answer to this question, it is perhaps an over-simplification of a complex issue. PfEMP1 is certainly the leading candidate for the parasite-encoded factor to which a protective and acquired immunity develops during repeated episodes of malaria in young childhood. There are, however, several other polymorphic proteins expressed on the surface of the infected erythrocyte (IE) that may also contribute to this phenomenon. Thus, PfEMP1 along with Rifins, Stevor and Surfins, amongst others, are collectively termed variant surface antigens (VSA) – which **together** are known to be the target of a protective immune response. To explore the specific contribution that PfEMP1 makes, Chan, Howell and colleagues describe an elegant study that dissects PfEMP1 away from the gamut of remaining VSA.

This team exploit an interesting molecular tool to generate genetically-modified parasites which they then use a clinical immunology study. PfEMP1 are encoded by a multigene family – termed *var*. Using epigenetic regulatory mechanism operating in part on the *var* promoter, only one *var* gene is expressed any time. Coupling a *var* promoter to a drug selectable marker and transfecting this into the parasite results in a transgenic parasite that does not express PfEMP1. This is because, in the presence of drug selection, the only *var* promoter turned on is that providing resistance to the drug– all other *var* promoters are off – and thus, no PfEMP1 is expressed.

Using these PfEMP1 knockout parasites, this team demonstrates;

- That IgG binding to PfEMP1 knockout parasites is reduced i.e. PfEMP1 is the predominant VSA in terms of antibody binding
- That IgG from older children (who are parasite positive on sampling) are more likely to bind the PfEMP1 positive IE, but not those where PfEMP1 is knocked out – i.e. the immunity acquired over time (and repeated infection) can be attributed to PfEMP1 recognition
- That an IgG-mediated immune response against PfEMP1 is protective – IgG that bind other VSA don't appear to be as protective
- The likely mechanism of protection is that IgG-PfEMP1 opsonised IE are more readily phagocytosed.

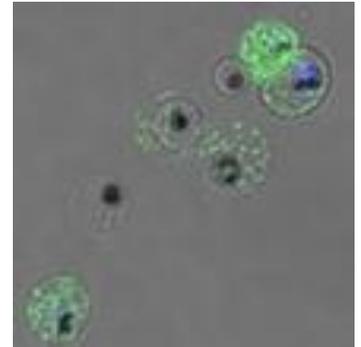
The outcomes from the study are perhaps not surprising to those closely involved in this field – although they in turn are perhaps more appreciative of the subtleties between VSA and PfEMP1. Understanding the relative contribution of PfEMP1 to VSA does help the community to move forward in using PfEMP1 in a vaccine. Whilst PfEMP1-vaccines are certainly a challenge, two factors mitigate this. First – as demonstrated in this report, PfEMP1 is the **natural** target of protective immunity. Second, as it appears that restricted subsets of PfEMP1 are expressed in patients with severe malaria, the diversity of PfEMP1 components needed to elicit some level of pan cross-PfEMP1 variant protection against the most severe consequences of infection may be more manageable than originally thought.

**Paul Horrocks is a Senior Lecturer at Keele University School of Medicine**

**Targets of antibodies against *Plasmodium falciparum*–infected erythrocytes in malaria immunity.** J Chan, KB Howell, L Reiling, R Ataide, C Mackintosh, F Fowkes, M Petter, J Chesson, C Langer, G Warimwe, M Duffy, S Rogerson, P Bull, A Cowman, K Marsh, J Beeson

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Figure citation: The kinetics of antibody binding to *Plasmodium falciparum* VAR2CSA PfEMP1 antigen and modelling of PfEMP1 antigen packing on the membrane knobs. Joergensen et al. *Malar J* 2010,9:100



*P. falciparum* infected erythrocytes exposed to IgG from an acute malaria patient, subsequently labelled using fluorochrome-conjugated anti-human IgG (from Joergensen et al. 2010)