

# Plasmodium falciparum erythrocyte membrane protein 1

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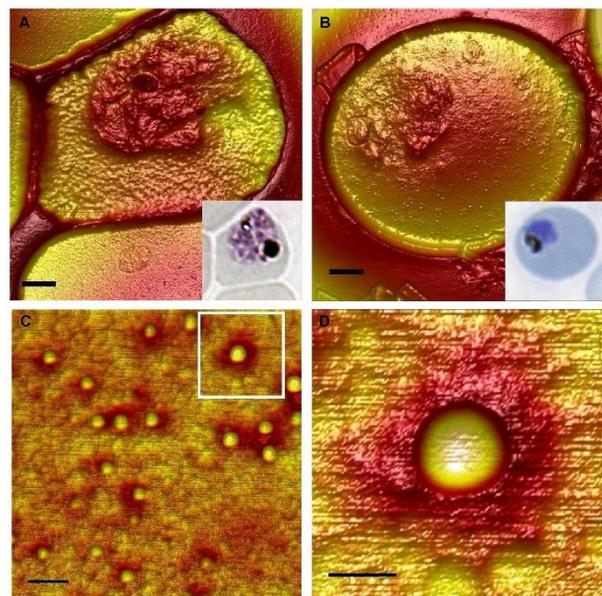
## Abstract

Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) is a family of proteins present on the membrane surface of red blood cells (RBCs or erythrocytes) that are infected by the malarial parasite Plasmodium falciparum. PfEMP1 is synthesized during the parasite's blood stage (erythrocytic schizogony) inside the RBC, during which the clinical symptoms of falciparum malaria are manifested. Acting as both an antigen and adhesion protein, it is thought to play a key role in the high level of virulence associated with *P. falciparum*. It was discovered in 1984 when it was reported that infected RBCs had unusually large-sized cell membrane proteins, and these proteins had antibody-binding (antigenic) properties. An elusive protein, its chemical structure and molecular properties were revealed only after a decade, in 1995. It is now established that there is not one but a large family of PfEMP1 proteins, genetically regulated (encoded) by a group of about 60 genes called var. Each *P. falciparum* is able to switch on and off specific var genes to produce a functionally different protein, rendering evasion from the host's immune system. RBCs carrying PfEMP1 on their surface stick to endothelial cells, which facilitates further binding with uninfected RBCs (through the processes of sequestration and rosetting), ultimately helping the parasite to both spread to other RBCs as well as bringing about the fatal symptoms of *P. falciparum* malaria.

**Keywords:** Plasmodium falciparum, PfEMP1, endothelium, red blood cell, var gene

## Introduction

Malaria is the deadliest among infectious diseases, accounting for approximately 429,000 human deaths in 2015 as of the latest estimate by the [World Health Organization](#).<sup>[2]</sup> In humans, malaria can be caused by five *Plasmodium* parasites, namely *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*.<sup>[3]</sup> *P. falciparum* is the most dangerous species, attributed to >99% of malaria's death toll, with 70% of these deaths occurring in children under the age of five years.<sup>[2]</sup> The parasites are transmitted through the bites of female mosquitos (of the species of *Anopheles*). Before invading the RBCs and causing the symptoms of malaria, the parasites first multiply in the liver. The daughter parasites called merozoites then only infect the RBCs. They undergo structural development inside the RBCs, becoming trophozoites and schizonts. It is during this period that malarial symptoms are produced.<sup>[4]</sup> Unlike RBCs infected by other *Plasmodium* species, *P. falciparum*-infected RBCs



**Figure 1 |** Images of RBCs infected by *P. falciparum* using atomic force microscopy. (A) An early schizont with cluster of knobs at the center. Scale bar = 1  $\mu$ m. Inset is the same image under light microscope. (B) A young trophozoite with knobs. Scale bar = 1  $\mu$ m. (C) A close up of the cell membrane showing individual knobs. Scale bar = 200 nm. (D) A close up of a single knob. Scale bar = 75 nm.<sup>[1]</sup>

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had been known to spontaneously stick together. By the early 1980s, it was established that when the parasite (both the trophozoite and schizont forms) enters the blood stream and infects RBCs, the infected cells form knobs on their surface (**Figure 1**). Then they become sticky, and get attached to the walls (endothelium) of the blood vessels through a process called cytoadhesion, or cytoadherence.<sup>[5]</sup> Such attachment favours binding with and accumulation of other RBCs. This process is known as sequestration.<sup>[6]</sup> It is during this condition that the parasites induce an immune response (antigen-antibody reaction) and evade destruction in the spleen.<sup>[7][8]</sup> Although the process and significance of sequestration were described in detail by two Italian physicians **Amico Bignami** and **Ettore Marchiafava** in the early 1890s, it took a century to discover the actual factor for the stickiness and virulence.<sup>[9][10]</sup>

## Discovery

PfEMP1 was discovered by **Russell J. Howard** and his colleagues at the US National Institutes of Health in 1984. Using the techniques of **radioiodination** and **immunoprecipitation**, they found a unique but yet unknown antigen from *P. falciparum*-infected RBCs that appeared to cause binding with other cells.<sup>[11]</sup> Since the antigenic protein could only be detected in infected cells, they asserted that the protein was produced by the malarial parasite, and not by RBCs. The antigen was large and appeared to be different in size in different strains of *P. falciparum* obtained from **night monkey** (*Aotus*). In one strain, called Camp (from Malaysia), the antigen was found to have a molecular size of approximately 285 kDa; while in the other, called St. Lucia (from El Salvador), it was approximately 260 kDa. Both antigens bind to cultured skin cancer (**melanoma**) cells. But the researchers failed to confirm whether or not the protein actually was an adhesion molecule to the wall of blood vessels.<sup>[12]</sup> Later in the same year, they found out that the unknown antigen was associated only with RBCs having small lumps called knobs on their surface.<sup>[13]</sup> The first human RBC antigen was reported in 1986. Howard's team found that the antigens from Gambian children, who were suffering from falciparum malaria, were similar to those from the RBCs of night monkey. They determined that the molecular sizes of the proteins ranged from 250 to 300 kDa.<sup>[14]</sup>

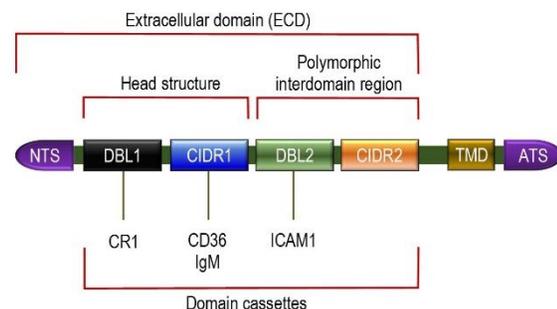
In 1987, they discovered another type of surface antigen from the same Camp and St. Lucia strains of malarial parasites. This was also a large-sized protein of about 300 kDa, but quite different from the antigens reported in 1984. The new protein was unable to bind to melanoma cells and present only inside the cell. Hence, they

named the earlier protein *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1), to distinguish it from the newly identified *Plasmodium falciparum* erythrocyte membrane protein 2 (PfEMP2).<sup>[15]</sup> The distinction was confirmed the next year, with an additional information that PfEMP1 is relatively less in number.<sup>[16]</sup>

Although some of the properties of PfEMP1 were firmly established, the protein was difficult to isolate due to its low occurrence. Five years after its discovery, one of the original researchers Irwin Sherman began to doubt the existence of PfEMP1 as a unique protein.<sup>[10]</sup> He argued that the antigen could be merely a surface protein of RBCs that changes upon infection with malarial parasites.<sup>[17]</sup> A consensus was achieved in 1995 following the identification (by **cloning**) of the gene for PfEMP1. The discovery of the genes was independently reported by Howard's team and two other teams at NIH. Howard's team identified two genes for PfEMP1, and **recombinant protein products** of these genes were shown to have antigenic and adhesive properties. They further affirmed that PfEMP1 is the key molecule in the ability of *P. falciparum* to evade the host's immune system.<sup>[18]</sup> Joseph D. Smith and others showed that PfEMP1 is actually a large family of proteins encoded by a multigene family called *var*. The gene products can bind to a variety of receptors including those on endothelial cells.<sup>[19]</sup> Xin-Zhuan Su and others showed that there could be more than 50 *var* genes which are distributed on different chromosomes of the malarial parasite.<sup>[20]</sup>

## Structure

PfEMP1 is a large family of proteins having high molecular weights ranging from 200 to 350 kDa.<sup>[21]</sup> The wide range of molecular size reflects extreme variation in the amino acid composition of the proteins. But all the PfEMP1 proteins can be described as having three basic structural components, namely, an extracellular domain (ECD), a transmembrane domain (TMD) and an intracellular acidic terminal segment (ATS) (**Figure 2**).



**Figure 2** | Typical structure of PfEMP1. NTS = N terminal segment. TMD = transmembrane domain. ATS = intracellular acidic terminal segment.

The extracellular domain is fully exposed on the cell surface, and is the most variable region. It consists of a number of sub-domains, including a short and conserved N terminal segment (NTS) at the outermost region, followed by a highly variable Duffy-binding-like (DBL) domain, sometimes a Ca<sup>2+</sup>-binding C2 domain, and then one or two cysteine-rich interdomain regions (CIDRs).<sup>[9][22]</sup>

Duffy-binding-like domains are so named because of their similarity to the Duffy-binding proteins of *P. vivax* and *P. knowlesi*.<sup>[23]</sup> There are six variant types of DBL, named DBL $\alpha$ , DBL $\beta$ , DBL $\gamma$ , DBL $\delta$ , DBL $\epsilon$  and DBL $\zeta$ . CIDR is also divided into three classes: CIDR $\alpha$ , CIDR $\beta$  and CIDR $\gamma$ .<sup>[24]</sup> Both DBL and CIDR have an additional type called PAM, so named because of their specific involvement in pregnancy-associated malaria (PAM).<sup>[25]</sup> In spite of the diverse DBL and CIDR proteins, the extracellular amino terminal region is partly conserved, consisting of about 60 amino acids of NTS, one each of DBL $\alpha$  and CIDR1 proteins in tandem. This semi-conserved DBL $\alpha$ -CIDR1 region is called the head structure.<sup>[26]</sup> The last CIDR region joins the TMD, which is embedded in the cell membrane. The TMD and ATS are highly conserved among different PfEMP1s.<sup>[27]</sup>

The head structure is followed by a variable combination of diverse DBL and CIDR proteins, and in many cases along with C2. This variation gives rise to different types of PfEMP1. The DBL-CIDR combination in a particular type of PfEMP1 protein is never random, but organized into specific sequences known as domain cassettes.<sup>[28]</sup> In some domain cassettes, there are only two or few DBL domains and CIDR domains, but in others they cover the entire length of the PfEMP1. These differences are responsible for different binding capacity among different PfEMP1s.<sup>[29]</sup> For instance, among the most well-known types, VAR3 (earlier called type 3 PfEMP1) is the smallest, consisting of only NTS with DBL1 $\alpha$  and DBL2 $\epsilon$  domains in the ECD. Its molecular size is approximately 150 kDa.<sup>[30]</sup> In domain cassette (DC) 4 type, the ECD is made up of three domains DBL $\alpha_{1.1/1.4}$ , CIDR $\alpha_{1.6}$  and DBL $\beta_3$ . The DBL $\beta_3$  domain contains a binding site for intercellular adhesion molecule 1 (ICAM1). This is particularly implicated with the development of brain infection.<sup>[31]</sup> VAR2CSA is atypical in having a single domain cassette that consists of three N terminal DBL<sub>PAM</sub> domains followed by three DBL $\epsilon$  domains and one CIDR<sub>PAM</sub>. The seven domains always occur together. The usual NTS is absent.<sup>[32][33]</sup> The protein specifically binds to chondroitin sulphate A (CSA); hence the name VAR2CSA.<sup>[34]</sup>

## Synthesis and transport

The PfEMP1 proteins are regulated and produced (encoded) by about 60 different *var* genes,<sup>[36]</sup> but an individual *P. falciparum* would switch on only a single *var* gene at a time to produce only one type of PfEMP1.<sup>[37][38]</sup> The *var* genes are distributed in two exons. Exon 1 encodes amino acids of the highly variable ECD,<sup>[39]</sup> while exon 2 encodes those of the conserved TMD and ATS.<sup>[40]</sup> Based on their location in the chromosome and sequence, the *var* genes are generally classified into three major groups, A, B, and C, and two intermediate groups, B/A and B/C,<sup>[9][41]</sup> or sometimes simply into five classes, *upsA*, *upsB*, *upsC*, *upsD*, and *upsE* respectively.<sup>[42]</sup> Groups A and B are found towards the terminal end (subtelomeric) region of the chromosome, while group C is in the central (centromeric) region.<sup>[43][44]</sup>

Once the PfEMP1 protein is fully synthesized (translated), it is carried to the cytoplasm towards the RBC membrane. The NTS is crucial for such directional movement.<sup>[26]</sup> Within the cytoplasm, the newly synthesized protein is attached to a Golgi-like membranous vesicle called the Maurer's cleft.<sup>[45]</sup> Inside the Maurer's clefts is a family of proteins called *Plasmodium* helical interspersed subtelomeric (PHIST) proteins. Of the PHIST proteins, PFI1780w and PFE1605w bind the intracellular ATS of PfEMP1 during transport to the RBC membrane.<sup>[46][47]</sup>

The PfEMP1 molecule is deposited at the RBC membrane at the knobs (Figure 3).<sup>[48]</sup> These knobs are easily identified as conspicuous bumps on the infected RBCs from the early trophozoite stage onward.<sup>[49]</sup> The malarial parasite cannot induce its virulence on RBCs without knobs.<sup>[50]</sup> As many as 10,000 knobs are distributed throughout the surface of a mature infected RBC, and each knob is 50-80 nm in diameter.<sup>[1]</sup> The export of pEMP1 from Maurer's cleft to RBC membrane is mediated by binding of another protein produced by the parasite called knob-associated histidine-rich protein

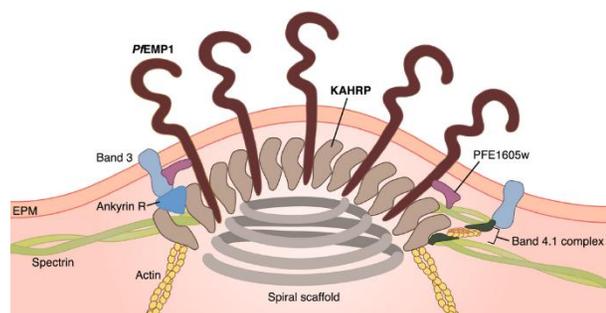


Figure 3 | Model of a knob structure of *P. falciparum*-infected RBC showing attachment of PfEMP1.<sup>[35]</sup>  
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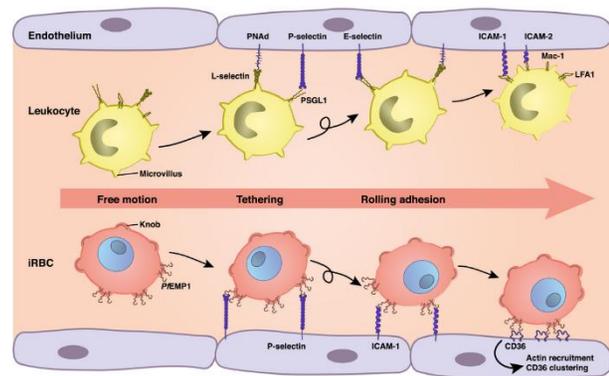
(KAHRP). KAHRP enhances the structural rigidity of infected RBC and adhesion of PfEMP1 on the knobs.<sup>[51]</sup> It is also directly responsible for forming knobs, as indicated by the fact that *kahrp* gene-deficient malarial parasites do not form knobs.<sup>[52]</sup> To form a knob, KAHRP aggregates several membrane skeletal proteins of the host RBC, such as spectrin, actin, ankyrin R, and spectrin-actin band 4.1 complex.<sup>[53]</sup> Upon arrival at the knob, PfEMP1 is attached to the spectrin network using the PHIST proteins.<sup>[54][35]</sup>

## Function

The primary function of PfEMP1 is to bind and attach RBCs to the wall of the blood vessels (**Figure 4**). The most important binding properties of *P. falciparum* known to date are mediated by the head structure of PfEMP1, consisting of DBL domains and CIDRs.<sup>[56]</sup> DBL domains can bind to a variety of cell receptors including thrombospondin (TSP), complement receptor 1 (CR1), chondroitin sulfate A (CSA),<sup>[5]</sup> P-selectin,<sup>[57]</sup> endothelial protein C receptor (EPCR),<sup>[58]</sup> and heparan sulfate.<sup>[59]</sup> The DBL domain adjacent to the head structure binds to ICAM1.<sup>[60]</sup> CIDRs mainly bind to a large variety of cluster determinant 36 (CD36).<sup>[21][61]</sup> These bindings produce the pathogenic characteristics of the parasite, such as sequestration of infected cells in different tissues,<sup>[62]</sup> invasion of RBCs,<sup>[63]</sup> and clustering of infected cells by a process called rosetting.<sup>[64]</sup>

CIDR1 protein in the semi-conserved head structure is the principal and best understood adhesion site of PfEMP1. It binds with CD36 on endothelial cells.<sup>[65][66]</sup> Only group B and C proteins are able to bind, and that too with only those having CIDR $\alpha$ 2-6 sequence types. On the other hand, group A proteins have either CIDR $\alpha$ 1 or CIDR $\beta/\gamma/\delta$ , and they are responsible for the most severe condition of malaria.<sup>[44]</sup> Binding with ICAM1 is achieved through the DBL $\beta$  domain adjacent to the head structure. However, many PfEMP1s having DBL $\beta$  domain do not bind to ICAM1,<sup>[67]</sup> and it appears that only the DBL $\beta$  paired with C2 domain can to bind to ICAM1.<sup>[62]</sup> The DBL $\alpha$ -CIDR $\gamma$  tandem pair is the main factor for rosetting (**Figure 5**),<sup>[55]</sup> sticking together the infected RBC with the uninfected cells, and thereby clogging of the blood vessels. This activity is performed through binding with CR1.<sup>[64][68]</sup>

The most dangerous malarial infection is in the brain and is called cerebral malaria. In cerebral malaria, the PfEMP1 proteins involved are DC8 and DC13. They are named after the number of domain cassettes they contain, and are capable of binding not only endothelial cells of the brain, but also in different organs including



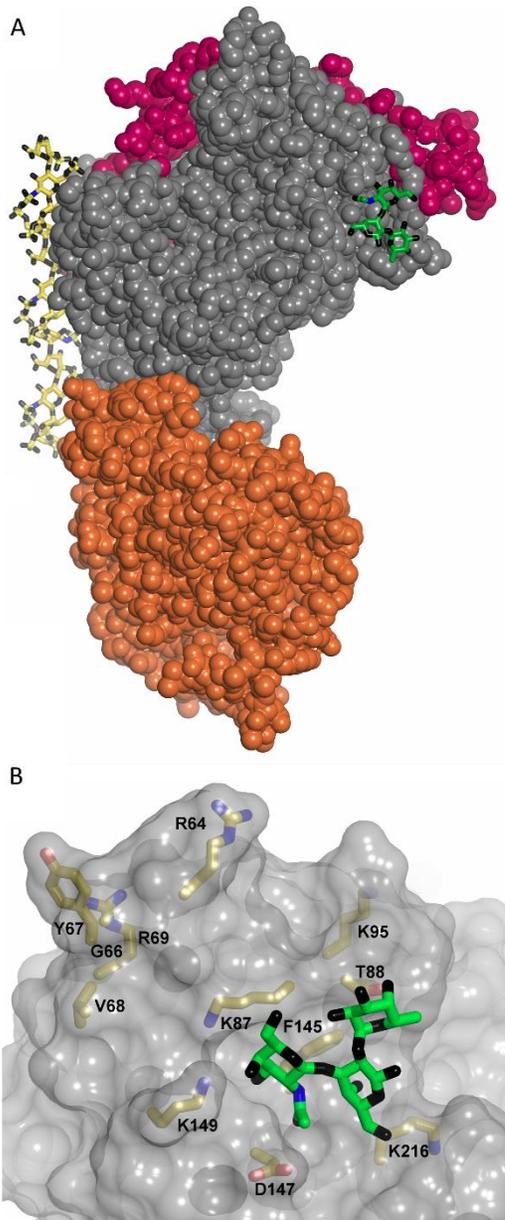
**Figure 4 |** Model of binding of RBC and WBC infected by *P. falciparum* to endothelial cells.<sup>[35]</sup>  
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brain, lung, heart, and bone marrow.<sup>[69]</sup> Initially, it was assumed that PfEMP1 binds to ICAM1 in the brain, but DC8 and DC13 were found incompatible with ICAM1. Instead DC8 and DC13 specifically bind to EPCR using CIDR $\alpha$  sub-types such as CIDR $\alpha$ 1.1, CIDR $\alpha$ 1.4, CIDR $\alpha$ 1.5 and CIDR $\alpha$ 1.7.<sup>[58]</sup> However, it was later shown that DC13 can bind to both ICAM1 and EPCR.<sup>[70]</sup> EPCR is thus a potential vaccine and drug target in cerebral malaria.<sup>[71]</sup>

VAR2CSA is unique in that it is mostly produced by the placenta during pregnancy (the condition called pregnancy-associated malaria, PAM, or placental malaria). The majority of PAM is therefore due to VAR2CSA.<sup>[27]</sup> Unlike other PfEMP1, VAR2CSA binds to chondroitin sulphate A present on the vascular endothelium of placenta. Although its individual domains can bind to CSA, its entire structure is used for complete binding.<sup>[72]</sup> The major complication in PAM is low-birth-weight babies. However, women who survived the first infection generally develop an effective immune response. In *P. falciparum*-prevalent regions in Africa, pregnant women are found to contain high levels of antibody (immunoglobulin G, or IgG) against VAR2CSA, which protect them the placenta-attacking malarial parasite. They are noted for giving birth to heavier babies.<sup>[73]</sup>

## Clinical importance

In a normal human immune system, malarial parasite binding to RBCs stimulates the production of antibodies that attack the PfEMP1 molecules. Binding of antibody with PfEMP1 disables the binding properties of DBL domains, causing loss of cell adhesion, and the infected RBC is destroyed. In this scenario, malaria is avoided.<sup>[74]</sup> However, to evade the host's immune response, different *P. falciparum* switch on and off different *var* genes to produce functionally different (antigenically distinct) PfEMP1s. Each variant type of



**Figure 5 |** The RBC-binding site of PfEMP1. (A) The head structure (mauve = NTS region, grey = DBL1 $\alpha$ 1, orange = CIDR1 $\gamma$ ) with the docked blood group A (green-blue-black sticks) and heparin (yellow-black sticks) molecules. (B) Detail of the RBC-binding site with bound molecules (yellow = C, blue = N, red = O).<sup>[55]</sup> Vigan-Womas et al. CC-BY-SA-4.0

PfEMP1 has different binding property, and thus, is not always recognized by antibodies.<sup>[75]</sup>

By default, all the *var* genes in the malarial parasite are inactivated. Activation (*gene expression*) of *var* is initiated upon infection of the organs. Further, in each organ only specific *var* genes are activated. The severity of the infection is determined by the type of organ in

which infection occurs, hence, the type of *var* gene activated. For examples, in the most severe cases of malaria, such as cerebral malaria, only the *var* genes for the PfEMP1 proteins DC8 and DC13 are switched on.<sup>[76][77]</sup> Upon the synthesis of DC8 and DC13, their CIDR $\alpha$ 1 domains bind to EPCR, which brings about the onset of severe malaria.<sup>[78]</sup> The abundance of the gene products (*transcripts*) of these PfEMP1 proteins (specifically the CIDR $\alpha$ 1 subtype transcripts) directly relates to the severity of the disease. This further indicates that preventing the interaction between CIDR $\alpha$ 1 and EPCR would be good target for a potential vaccine.<sup>[79][80]</sup> In pregnancy-associated malaria, another severe type of falciparum malaria, the gene for VAR2SCA (named *var2csa*) is activated in the placenta. Binding of VAR2SCA to CSA is the primary cause of premature delivery, death of the foetus and severe anaemia in the mother.<sup>[72]</sup> This indicates that drugs targeting VAR2SCA will be able to prevent the effects of malaria, and for this reason VAR2SCA is the leading candidate for development of a PAM vaccine.<sup>[81]</sup>

## Acknowledgements

Conflict of Interest: none declared.

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