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(54) **METHOD AND COMPOSITIONS FOR PREVENTION AND TREATMENT OF MALARIA INFECTIONS**

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(57) **ABSTRACT**

Isolated proteins and nucleic acid sequence encoding such protein that interacts with a red blood cell to be invaded by a malaria parasite and link with a component of the actin-myosin based machinery of the malaria parasite are provided. In addition methods for identifying agents which inhibit the function of these proteins as chemotherapeutic and/or immunologic agents for treatment and prevention of malaria infections are provided. Compositions for treatment and prevention of malaria infections and methods for preventing and treating malaria infections are also provided.

METHOD AND COMPOSITIONS FOR PREVENTION AND TREATMENT OF MALARIA INFECTIONS

[0001] This patent application claims the benefit of priority from U.S. Provisional Application Ser. No. 60/628,572 filed Nov. 17, 2004, teachings of which are herein incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] A protein, referred to herein as PfMTI-1, and orthologs thereof have now been identified as providing a key molecular link for malaria parasites between the red blood cell, which is to be invaded, and the actin myosin based motor machinery of the parasite that drives the invasion process. Inhibition of the function of this protein or a homolog or ortholog thereof or a nucleic acid encoding this protein or a homolog or ortholog thereof prevents the parasite from invading red blood cells and is expected to prevent or lessen the clinical severity of malaria infection. Accordingly, the present invention provides methods for development of compositions for use in immunologic and chemotherapeutic therapies for treatment and prevention of malaria. Compositions and methods for use of these compositions in the treatment and prevention of malaria are also provided.

BACKGROUND OF THE INVENTION

[0003] Presently, malaria is a significant burden on humans. The parasite responsible for this disease continues to develop resistance to antimalarial drugs and there is no suitable vaccine to control the disease. These two major features ensure that malaria remains a major global health problem. *Plasmodium falciparum* causes the most severe form of the disease in humans and is responsible for 200-300 million infections per year. Greater than two million people die as a result of the disease annually. The development of an effective vaccine and the development of new and inexpensive antimalarial drugs remain top priorities in the world health community.

[0004] A key process to target for both vaccine and drug development research is the process of parasite invasion. Of the various forms of the parasite, three stages must have the ability to invade host cells: the ookinete, the sporozoite and the merozoite. There are both common features as well as unique features during the invasion process by each form. For example, although the invasive stages of the parasite are morphologically and biochemically different from one another, they share a highly conserved structural organization and special organelles called micronemes and rhopteries (for review see Sinnis and Sini, Trends in Microb. 1997 5:52-58; Pinder et al, J. Cell Sci. 2000 111:1831-1839; Chitnis, C. E. Curr. Op. in Hemat. 2001 8:85-91; and Mota and Rodriquez, Bioessays 2002 24:149-156). While function of these conserved structures has not been fully clarified, it is known that they are required for host cell invasion. All of these common structures confer some similarity to target cell invasion; the specific details in each case, however, differ. Each invasive stage of the parasite has a different target cell specificity, which is believed to be governed by a specific receptor-ligand type interaction. Furthermore, the invasion of the host cell appears to be an active process, which requires an actin-myosin based motility system to enter the host cell (Pinder et al, J. Cell Sci. 2000 111:1831-1839 and Morrissette and Sibley Microb. Mol. Bio. Rev. 2002 66:21-38).

[0005] In the case of hepatocyte invasion by sporozoites, injection of a very small number of *Plasmodium* sporozoites is sufficient to initiate infection, suggesting that the invasion process is extremely efficient. Furthermore, the process of hepatocyte invasion is extremely rapid, occurring within minutes after the infectious bite of the mosquito. The efficiency and rapidity of sporozoite invasion suggests that it involves specific interactions between parasite-encoded surface proteins and host molecules. Several lines of evidence suggest that the circumsporozoite protein (CS) plays a key role in this process (Stewart et al. Infect. Immunol. 1986 51:859-864; Stewart and Vanderberg J. Protozol. 1988 35:389-393; Menard, R. Cell Microb. 2001 3:63-73; Mota and Rodriquez Bioessays 2002 24:149-156). The CS protein of all *Plasmodium* species contains a highly conserved region, called region H, that is also found in the type I repeats of thrombospondin and some other adhesion molecules. It is believed that region H of CS binds to glycosaminoglycan chains of heparin sulfate proteoglycans (HSPGS) that are found on the surface of hepatocytes (Sinnis et al. J. Exp. Med. 1994 180: 297-306). This binding is required for sporozoite attachment to hepatocytes, but is not necessary for invasion. Subsequent invasion with formation of a parasitophoros vacuole is tightly associated with exocytosis of the apical organelles. The attachment of the parasite to the host cell also triggers a transient cytosolic Ca^{2+} increase that is required for invasion. This increase in the Ca^{2+} concentration seems to induce the exocytosis of micronemes, a process required for the formation of the moving junction and the internalization of the parasite. Whether this increase in Ca^{2+} concentration is also required for activation of the actin-myosin based motility system, as seen with other non-Apicomplexan motility systems, is not known. The exocytosis of the apical organelles results in the release of the TRAP (Thrombospondin-related anonymous protein) molecule and its distribution along the surface of the sporozoite. TRAP is a transmembrane protein that contains two well-characterized adhesive modules, an A domain of Von Willebrand factor and a type 1 repeat of thrombospondin, in its extracellular domain. TRAP (−) parasites, created by gene-targeting technology in *Plasmodium*, are unable to invade mosquito salivary glands or infect liver cells in vivo after intravenous injection, suggesting that TRAP plays a key role in the invasion process (Sultan et al. Mol. Biochem. Parasitol. 1997 113:151-156). A structurally related molecule, *Plasmodium* CTRP, produced by the ookinete stage, probably plays a similar role as inactivation of CTRP in *Plasmodium berghei* and *Plasmodium falciparum* showed that CTRP is necessary for ookinete transformation into an oocyst, a stage of the life cycle that requires ookinete migration through the midget epithelium of the mosquito (Dessens et al. EMBO J. 1999 18:6221-6227; Yuda et al. J. Exp. Med. 1999 190:1711-1715; Templeton et al. Mol. Microb. 2000 36:1-9).

[0006] The merozoite form of the asexual life cycle in the blood stage attaches to the surface of the red blood cell (RBC) which initiates the invasion process of this host cell. Many of the surface proteins of the merozoite are thus exposed to the immune system and consequently are potential vaccine candidates. Many of these proteins are thought to play a role in merozoite invasion of RBCs but the details of their function and interactions remain unclear at best. Merozoite invasion takes place following initial interaction with the RBC surface

followed by re-orientation to allow the apical end of the parasite to interact with the membrane of the host cell. This re-orientation allows the contents of the apical organelles to be released and a tight junction is formed between the merozoite surface and the RBC membrane. The tight junction moves along the surface of the merozoite, possibly via force generated by the actin-myosin motor, until the membrane fuses at the posterior end of the parasite, resulting in the formation of the parasitophorous vacuole contain the newly invaded parasite (Pinder et al. Parasit. Today 2000 16:240-245). While multiple proteins appear to be involved in this complex process of RBC invasion, very little is known about the particular role of any individual protein in the process. One of the surface proteins, merozoite surface protein I (MSPI) has been postulated to be involved in the initial interaction of the merozoite with the RBC surface (Holder and Freeman, J. Exp. Med. 1984 160:624-629; Holder et al. Nature 1985 317:270-273; Perkins and Rocco J. Immunol. 1988 141:3190-3196). The localization of this GPI-anchored protein is shared with a number of other GPI-linked proteins including MSP2, MSP4 and MSP5 (Smythe et al. Proc. Natl Acad. Sci. USA 1988 85:5195-5199; Marshall et al. Infect. Immun. 1997 65:4460-4467; Marshall et al. Mol. Biochem. Parasitol. 1998 94:13-25). Apical membrane antigen I (AMA I) is an integral membrane protein that is initially localized to the neck of the rhoptries although it re-distributes onto the surface of the merozoite (Deans et al. Mol. Biochem. Parasitol. 1984 11:189-204; Peterson et al. Mol. Cell Biol. 1989 9:3151-3154; Narum and Thomas Mol. Biochem. 1994 67:59-68; Marshall et al. Mol. Biochem. Parasitol. 1989 27:281-284; Peterson et al. Mol. Cell Biol. 1990 9:3151-3154). The function of AMAI is presently unknown. Within the rhoptries, a number of proteins have been identified that may be involved in the invasion process. These include the rhoptry-associated proteins 1 and 2 (RAP I and RAP2) (Ridley et al. Mol. Biochem. Parasitol. 1990 41:125-134; and Perrin et al. J. Clin. Invest. 1985 75:1718-1721). The soluble complex of these two molecules is delivered out to the rhoptries during invasion and is carried through into the parasitophorous vacuole (Baldi et al. EMBO J. 2000 19:1-9). The erythrocyte-binding antigen 175 (EBA 175) of *Plasmodium falciparum* is located in the micronemes and has been shown to bind to the RBC surface molecule glycophorin A in a sialic acid-dependent manner (Sim et al. Exp. Parasit. 1992 78:259-268; Wu et al. Proc. Natl Acad. Sci. USA 1996 93:1130-1134; Crabb et al. Cell 1997 89:287-296). Disruption of the gene encoding EBA175 to investigate the role of the conserved carboxy-terminal cysteine-rich domain, the transmembrane domain and the cytoplasmic domain suggested these regions were not essential for merozoite invasion (Reed et al. Proc. Natl Acad. Sci USA 2000 97:7509-7514). However, analysis of RBC invasion with these mutants suggested that the EBA175/glycophorinA pathway was disrupted. It appears that the mutant parasites now invaded using a sialic-acid independent pathway suggesting that the parasite has the ability to utilize alternative pathways for invasion of RBCs.

[0007] The involvement of an actin-myosin-based motor in invasion was suggested by Miller et al. based upon studies of the effect of cytochalasin B on *Plasmodium* invasion (Miller et al. J. Exp. Med. 1979 149:172-184). In *Plasmodium*, there are two genes for actin. Actin I is intronless and is expressed throughout the parasite life cycle, wherein actin II has an intron and is transcribed only in the sexual stages (Wesseling et al. Mol. Biochem. Parasitol. 1988 27:313-320; Wesseling et al. Mol. Biochem. Parasit. 1988 27:313-320, Wesseling et al. Mol. Biochem. Parasitol. 1989 35:167-176). The amino acid sequence of actin II diverges from previously characterized actins exhibiting only 79% sequence similarity to the sequence of actin I (Wesseling et al. Mol. Biochem. Parasit. 1988 27:313-320). The majority of actin in Apicomplexan parasites appears to be monomeric rather than being in the polymerized form. Localization studies using anti-actin antibodies have indicated that actin is present in the region between the plasma membrane and the inner membrane complex (IMC), which is composed of two closely aligned membranes. The involvement of myosin in Apicomplexan invasion was suggested by Dobrowski et al. and Pinder et al. based upon studies where invasion was reversibly inhibited by the myosin ATPase inhibitor butane-2,3-monoxime (Dobrowski et al. Mol. Microbiol. 1997 26:163-173; Pinder et al. J. Cell Sci. 1998 111:1831-1839). As in other species, *Apicomplexa* contains several myosin genes. Of these, MyoA has been disclosed as rather unique (Heintzehnan and Schwartzman J. Parasitol. 1997 87:429-432). This myosin is expressed in all *Plasmodium* invasive stages. The molecule is very small (approximately 90 kD) but the head domain displays the universally conserved ATP and actin binding sites. MyoA binds actin and actin is released in an ATP-dependent fashion. However, MyoA has several unique features, including virtually no recognizable neck domain (which is normally the binding site for a canonical myosin light chain) and a very short carboxy terminal tail. In the mature merozoite, MyoA is peripherally located with most staining occurring at the apical end and electron microscopy indicates that it is also located between the plasma membrane and the RAC (Pinder et al. J. Cell Sci. 1998 111:1831-1839).

[0008] Using a yeast two-hybrid system (Fields and Song Nature 1989 340:245-248; Luban and Goff Curr. Opin. Biotech. 1995 6:59-65), a molecule termed MTIP (MyoA Tail Interacting Protein) was isolated. This molecule binds to the short carboxy terminal tail of MyoA. Studies on the localization of this molecule have led to the proposal of a new model for the organization of the actin-myosin based machinery located between the plasma membrane and the IMC (Bergman et al. J. Cell Sci. 2003 116:39-49). It is believed that the "moving junction" which forms during invasion is a circumferential zone of attachment at the opening of the host cell invagination. This zone is characterized by a markedly thickened host cell membrane with increased electron density and is frequently accompanied by a constriction in the parasite body. The parasite enters the newly forming parasitophorous vacuole by capping the moving junction down its body. Eventually, the parasite becomes enclosed within a cavity delimited by the invaginated host cell membrane (Aikawa et al. J. Cell Bio. 1978 77:72-82; Michel et al. Int. J. Parasitol. 1980 10:309-313). The moving junction is a highly specialized interface of the parasite with the host cell, presumably utilizing cytoskeletal proteins, signaling molecules and receptors. However, very little is known about this interface. The protein MCP-I (Merozoite Capping Protein-1) was localized initially at the attachment site formed between the merozoite apical region and the erythrocyte (Klotz et al. Mol. Biochem. Parasitol. 1989 36:177-185). During the invasion process, MCP-1 migrates around merozoites in an anterior-to-posterior movement to finally persist at the posterior end of the newly invaded parasite (at the end nearest the erythrocyte membrane). MCP-1 is a 415 amino acid protein but interestingly is detected as a 60 kD protein in extracts from blood stage

parasites. The amino terminal third of the molecule is an oxido-reductase domain but the function of this domain is not known. Thus, it appears that MCP-1 is localized to the moving junction in invading parasites but its role and potential interactions with other molecules remains unclear,

[0009] A new protein, *Plasmodium falciparum* Merozoite TRAP-like Invasin 1, referred to herein as PfMTI-1, has now been isolated and characterized. Blockage or inhibition of this protein is believed to prevent the malaria parasite from invading red blood cells, thus preventing or lessening the clinical severity of the disease. This protein and homologs or orthologs thereof serve as prime targets for immunologic and chemotherapeutic intervention.

SUMMARY OF THE INVENTION

[0010] An aspect of the present invention relates to an isolated protein referred to herein as PfMTI-1, of the malaria parasite *Plasmodium falciparum* and homologs or orthologs thereof that interact with a red blood cell to be invaded by the parasite and link with a component of the actin-myosin based machinery of the malaria parasite.

[0011] Another aspect of the present invention relates to isolated nucleic acid sequences encoding the protein PfMTI-1 of the malaria parasite *Plasmodium falciparum* and homologs or orthologs thereof that interact with a red blood cell to be invaded by the parasite and link with a component of the actin-myosin based machinery of the malaria parasite.

[0012] Another aspect of the present invention relates to isolated antibodies which specifically bind the protein PfMTI-1 or a homolog or ortholog thereof, or a fragment thereof.

[0013] Another aspect of the present invention relates to a method for identifying potential therapeutic agents for malaria which comprises assessing the ability of a potential therapeutic agent to inhibit the function of the PfMTI-1 protein or a homolog or ortholog thereof thereby inhibiting the interaction of this protein with a red blood cell to be invaded by the malaria parasite and/or its linkage to a component of the actin-myosin based machinery of the malaria parasite.

[0014] Another aspect of the present invention relates to compositions and methods for inhibiting or preventing invasion of red blood cells by a malaria parasite. Compositions of the present invention comprise an agent which inhibits interaction of PfMTI-1 or an ortholog thereof with a host red blood cell and/or linkage to a component of actin-myosin based machinery of the malaria parasite. Methods of the present invention comprise administering this composition as a chemotherapeutic agent to a subject infected with a malaria parasite or as an immunologic agent to prevent infection in subjects at risk for infection by a malaria parasite.

Description of the Sequence Listing

[0015] SEQ ID NO: 1 and SEQ ID NO:2 are the amino acid sequence and the nucleic acid sequence, respectively, of PfMTI-1 isolated from *Plasmodium falciparum* strain 3D7.

[0016] SEQ ID NO:3 and SEQ ID NO:4 are the amino acid sequence and the nucleic acid sequence, respectively, of PfMTI-1 isolated from *Plasmodium falciparum* strain FVO.

[0017] SEQ ID NO:5 and SEQ ID NO:6 are the amino acid sequence and the nucleic acid sequence, respectively, of PfMTI-1 from *Plasmodium falciparum* strain D10.

[0018] SEQ ID NO:7 and SEQ ID NO:8 are the amino acid sequence and the nucleic acid sequence, respectively, of PfMTI-1 isolated from *Plasmodium falciparum* strain HB3.

[0019] SEQ ID NO:9 and SEQ ID NO:10 are the amino acid sequence and the nucleic acid sequence, respectively, of PfMTI-1 isolated from *Plasmodium falciparum* strain M24.

[0020] SEQ ID NO: 11 and SEQ ID NO: 12 are the amino acid sequence and the nucleic acid sequence, respectively, of PfMTI-1 isolated from *Plasmodium falciparum* strain MCAMP.

[0021] SEQ ID NO: 13 and SEQ ID NO: 14 are the amino acid sequence and the nucleic acid sequence, respectively, of PfMTI-1 isolated from *Plasmodium falciparum* strain C2A.

[0022] SEQ ID NO: 15 is an orthologous amino acid sequence to PfMTI-1 isolated from *Plasmodium vivax.*

[0023] SEQ ID NO: 16 an orthologous amino acid sequence to PfMTI-1 isolated from *Plasmodium knowlesi.*

DETAILED DESCRIPTION OF THE INVENTION

[0024] All invasive forms of the human malaria parasite (*Plasmodium falciparum*) must have a protein that serves as a molecular bridge or link between the host cell that is being invaded and the motor machinery of the parasites that drives the invasion process. The bridging or linking protein of the merozoite, the invasive form of the asexual or blood stage of the parasite life cycle that interacts with the red blood cell to be invaded and links with a component of the actin-myosin based motor machinery of the parasite has now been identified. Exemplary amino acid sequences of this protein, *Plasmodium falciparum* Merozoite TRAP-like Invasion 1, referred to herein as PfMTI-1, are depicted in SEQ ID NO: 1, 3, 5, 7, 9, 11 and 13. SEQ ID NO: 1 is the amino acid sequence of the protein isolated from *P. falciparum* strain 3D7. SEQ ID NO:3 is the amino acid sequence of the protein isolated from *P. falciparum* strain FVO. SEQ ID NO:5 is the amino acid sequence of the protein isolated from *P. falciparum* strain D10. SEQ ID NO:7 is the amino acid sequence of the protein isolated from *P. falciparum* strain HB3. SEQ ID NO:9 is the amino acid sequence of the protein isolated from *P. falciparum* strain M24. SEQ ID NO: 11 is the amino acid sequence of the protein isolated from *P. falciparum* strain MCAMP. SEQ ID NO: 13 is the amino acid sequence of the protein isolated from *P. falciparum* strain C2A. Nucleic acid sequences encoding the PfMTI-1 protein of strains 3D7, FVO, D10, HB3, M24, MCAMP and C2A are depicted in SEQ ID NO:2, 4, 6, 8, 10, 12 and 14, respectively.

[0025] This protein was identified using a bioinformatic approach to search for blood stage receptors in a *P. falciparum* predicted gene product database. Search criteria used allowed for the presence of an additional trans-membrane domain (signal sequence and two trans-membrane domains) as the computer can predict a trans-membrane domain from merely a stretch of hydrophobic domains. Only 6 proteins of *P. falciparum* met all criteria, one of which is PfMTI-1.

[0026] PfMTI-1 of the various strains comprises 488 to 503 amino acids and contains a signal sequence, a single trans-membrane domain, a thrombospondin domain and an acidic cytoplasmic domain with a tryptophan residue near the carboxy-terminus (residue 495 of 3D7). Using microarray data, PfMTI-1 was identified as being expressed in late stage parasites. Further, examination of other genes with a similar pattern of expression revealed that PfMTI-1 is expressed at the same approximate time during the parasite cell cycle as other molecules involved in the invasion process, such as PfMYOA

(*Plasmodium falciparum* Myosin A, Pinder et al, J. Cell Sci. 2000 111:1831-1839), PfMTIP (*Plasmodium falciparum* Myosin A Tail Interacting Protein, Bergman et al. J. Cell Sci. 2003 116:39-49) and PfAMA1 (*Plasmodium falciparum* Apical Membrane Antigen 1, Hodder et al, Infect. Immun. 2001 69:3286-3294). It is believed that this protein serves as the molecular bridge or link between a host erythrocyte being invaded by the malaria parasite and the motor machinery of the malaria parasite that drives the infection process.

[0027] The carboxy-terminal 44 amino acids of PfMTI-1 are expressed as a histidine-tagged recombinant protein and are incubated in an in vitro binding assay with recombinant Pf Aldolase (expressed as a glutathione-S-transferase fusion protein). The binding of the GST-aldolase fusion to the PfMTI-1 protein is specifically detected by incubation with an antibody directed against the GST moiety of the fusion protein and subsequent incubation with a conjugation secondary antibody. Furthermore, the specificity of the binding to Pf aldolase has been demonstrated using a similar histidine-tagged PfMTI-1 recombinant protein containing a tryptophan→alanine change at the fourth position from the carboxy-terminus of PfMTI-1. This result implicates PfMTI-1 as being a link between the plasma membrane of the parasite and the actin-myosin motor required for the invasion of red blood cells. This link between PfMTI-1 and Pf actin is indirect via the bridging molecule, Pf aldolase. Thus, inhibition of the function of the extracellular domain of PfMTI-1 or the interaction between PfMTI-1 and Pf aldolase may block the ability of the parasite to invade red blood cells.

[0028] Thus, the present invention provides an isolated malaria protein, PfMTI-1, and isolated homologs or orthologs thereof, now characterized as functioning as the molecular bridge or link between a host red blood cell that is being invaded and the motor machinery of the parasite that drives the invasion process. The amino acid sequence of exemplary PfMTI-1 proteins of the present invention which function as the molecular bridge or link between a host red blood cell that is being invaded and the motor machinery of the parasite that drives the invasion process are depicted in SEQ ID NO: 1, 3, 5, 7, 9, 11 and 13.

[0029] Based upon these exemplary amino acid sequences and the activity now taught herein for this protein, those skilled in the art can now routinely identify variant amino acid sequences, homologous or orthologous amino acid sequences and fragments of this exemplary amino acid sequence as well as fragments of variant and homologous or orthologous amino acid sequences exhibiting similar binding capabilities and/or activities with respect to host red blood cells and/or a component of the actin-myosin based motor machinery of the malaria parasite. Using such techniques, the inventors have identified orthologous proteins in *P. vivax* (SEQ ID NO:15) and *P. knowlesi* (SEQ ID NO:16).

[0030] The present invention also provides isolated nucleic acid sequences encoding PfMTI-1 and isolated homologs or orthologs, or fragments thereof. Exemplary nucleic acid sequences encoding PfMTI-1 are depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12 and 14. As will be understood by those skilled in the art, however, due to degeneracy in the genetic code, additional nucleic acid sequences may encode this protein. Identification of these degenerative sequences can be performed routinely by those skilled in the art based upon the teachings herein. Accordingly, these additional degenerate nucleic acid sequences as well as isolated nucleic acid sequences encoding homologs or orthologs of PfMTI-1 are also encompassed within the scope of this invention.

[0031] By the term "isolated", as used herein, it is a meant a protein or fragment thereof, or a nucleic acid sequence that is (1) no longer associated with naturally associated components that accompany it in its native state, (2) is free of other proteins or nucleic acid sequences from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a protein or fragment or nucleic acid sequence that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A protein or fragment thereof or a nucleic acid sequence may also be rendered substantially free of naturally associated components by isolation, using protein or nucleic acid sequence purification techniques well-known in the art.

[0032] By "homolog" or "homologous" when referring to a protein of the present invention it is meant proteins from different organisms with a similar sequence to the encoded amino acid sequence of PfMTI-1 and a similar biological activity or function. Although two proteins are said to be "homologous," this does not imply that there is necessarily an evolutionary relationship between the proteins. Instead, the term "homologous" is defined to mean that the two proteins have similar amino acid sequences and similar biological activities or functions. In a preferred embodiment, a homologous protein is one that exhibits 50% sequence similarity to PfMTI-1, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are homologous proteins that exhibit 80%, 85% or 90% sequence similarity to PfMTI-1. In a yet more preferred embodiment, a homologous protein exhibits 95%, 97%, 98% or 99% sequence similarity.

[0033] Most preferred is an ortholog or orthologous protein, meaning that the homologous proteins have a common ancestral species.

[0034] The term "fragment" as used herein with respect to proteins of the present invention refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion compared to the full-length PfMTI-1 protein or a homolog or ortholog thereof. In a preferred embodiment, the fragment is a contiguous sequence in which the amino acid sequence of the fragment is identical to the corresponding positions in the naturally-occurring PfMTI-1 protein, or homolog or ortholog thereof. Fragments typically are at least 5, 6, 7, 8, 9 or 10 amino acids long, preferably at least 12, 14, 16 or 18 amino acids long, more preferably at least 20 amino acids long, more preferably at least 25, 30, 35, 40 or 45, amino acids, even more preferably at least 50 or 60 amino acids long, and even more preferably at least 70 amino acids long. Most preferably, the fragment is of sufficient length to mimic the binding capability and/or activities of the full length protein.

[0035] The present invention also relates to derivatives of the PfVN-291 protein and homologues, orthologues and fragments thereof

[0036] A "derivative" when used herein with respect to proteins of the present invention refers to a modified protein substantially similar in primary structural sequence to PfMTI-1 or a homolog or ortholog thereof but which includes, e.g., in vivo or in vitro chemical and biochemical modifications that are not found in the naturally occurring proteins. Examples of such modifications include, but are in no way limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment

of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Other modifications include, for example, labeling with a detectable label such as a radionuclide, a fluorophore or an enzyme.

[0037] The present invention also provides isolated antibodies which specifically bind PfMTI-1 or a homolog or ortholog thereof or a fragment of PfMTI-1 or a homolog or ortholog thereof. The term "antibody" as used herein refers to an intact immunoglobulin, or to an antigen-binding portion of an immunoglobulin that competes with the intact antibody for specific binding to a protein or fragment of a protein of the present invention. Antigen-binding portions of an immunoglobulin of the present invention can be produced by various techniques including, but not limited to recombinant DNA techniques and enzymatic or chemical cleavage of intact antibodies. Exemplary antigen-binding portions include Fab, Fab', $F(ab')_2$, Fv, dAb, and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. Fab fragments are monovalent fragments consisting of VL, VH, CL and CH1 domains. $F(ab')_2$ fragments are bivalent fragments comprising two Fab fragments linked by a disulfide bridge at the hinge region. Fd fragments comprise a VH and CH1 domain. Fv fragment comprise a VL and VH domain of a single arm of an antibody. dAb fragments comprise a VH domain (Ward et al., Nature 1989 341: 544-546).

[0038] Antibodies of the present invention may be single-chain antibodies (scFv), meaning an antibody in which VL and VH regions are paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain (Bird et al., Science 1988 242: 423-426; Huston et al., Proc. Natl. Acad. Sci. USA 1988 85: 5879-5883). Antibodies of the present invention may also be diabodies, meaning bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (Holliger et al., Proc. Natl. Acad. Sci. USA 1993 90: 6444-6448; Poljak et al. 1994 Structure 2: 1121-1123). Further, one or more CDRs can be incorporated into a molecule either covalently or noncovalently to produce an immunoadhesin. An immunoadhesin may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the immunoadhesin to specifically bind to a particular antigen of interest, in this case PfMTI-1 or a homolog or ortholog thereof. A chimeric antibody is an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies.

[0039] An "isolated antibody" as used herein is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. It is known that purified proteins, including purified antibodies, may be stabilized with non-naturally-associated components. The non-naturally-associated component may be a protein, such as albumin (e.g., BSA) or a chemical such as polyethylene glycol (PEG).

[0040] By "bind specifically" and "specific binding" as used herein it is meant the ability of an antibody of the present invention to bind to a first molecular species in preference to binding to other molecular species with which the antibody and first molecular species are admixed. An antibody is said specifically to "recognize" a first molecular species when it can bind specifically to that first molecular species. In the present invention the first molecular species comprises PfMTI-1 or a homolog or ortholog thereof or a fragment of PfMTI-1 or a homolog or ortholog thereof.

[0041] Identification of PfMTI-1 and homologs and orthologs thereof can be used to design and/or identify therapeutic agents which prevent infection by malaria parasites and/or decrease the severity of clinical.

[0042] For example, the structure of these proteins can be used in computer modeling programs to design mimetics of PfMTI-1 and homologs or orthologs thereof. By "mimetic" it is meant to include peptide based compounds, also referred to as peptidomimetics, as well as small organic molecules. Preferably mimetics of the present invention are designed to bind to either the erythrocyte binding site of PfMTI-1 or the component of the actin-myosin based motor machinery of the malaria parasite to which PfMTI-1 binds, thereby inhibiting the ability of PfMTI-1 or homologs or orthologs thereof to form a molecular bridge between red blood cells and the parasite.

[0043] Identification of PfMTI-1 and its function can also be used in the development of high throughput screening assays to identify potential chemotherapeutic agents which inhibit the function of this protein and orthologs or homologs thereof, thereby decreasing severity of the clinical symptoms of malaria infections. In vitro binding assays, in a high throughput format could be developed to screen for agents that disrupt or prevent the binding of PfMTI-1 to parasite aldolase. These agents would then be screen in culture for their effect on the in vivo growth or invasion of *Plasmodium falciparum*. Alternatively, an agent may be isolated that blocks the presumptive interaction between PfMTI-1 and a component on the surface of the red cell. Again, similar assay would be utilized to screen the efficacy of the agent in vivo.

[0044] Further, this protein and homologs or orthologs thereof serve as prime targets for vaccine development against malaria infection. A useful vaccine will comprise an antigen capable of invoking an immune response against the PfMTI-1 protein or an ortholog or homolog thereof. Exemplary antigens include, but are not limited to the entire PfMTI-1 sequence, the exocellular domain of PfMTI-1, or regions thereof.

[0045] Thus, the present invention also provides methods for identifying potential therapeutic agents for malaria which comprises assessing the ability of a potential therapeutic to inhibit the function of the PfMTI-1 protein or an ortholog or homolog thereof thereby inhibiting the interaction of this

protein with a red blood cell to be invaded by the malaria parasite and/or its linkage to a component of the actin-myosin based machinery of the malaria parasite. Agents may inhibit the function directly by acting on the protein or protein's binding site or indirectly by invoking an immune response against the protein.

[0046] Further, agents identified as inhibiting the function of the PfMTI-1 protein or an ortholog or homolog thereof are expected to be useful in inhibiting and/or preventing malaria infections. Thus, the present invention also provides compositions and methods for inhibiting or preventing invasion of red blood cells by a malaria parasite.

[0047] Compositions of the present invention comprise an agent, which inhibits interaction of PfMTI-1 or an ortholog or homolog thereof with a host red blood cell and/or linkage to a component of actin-myosin based machinery of the malaria parasite in a pharmaceutically acceptable carrier. Selection of a pharmaceutically acceptable carrier for use in these compositions can be performed routinely by those of skill in the art based upon the solubility characteristics of the agent, its mode of action and the mode of administration desired for the composition. For example, if the agent is a vaccine typically administered via intramuscular injection, the carrier may comprise a sterile aqueous vehicle such as sterile saline or sterile phosphate buffered saline and may further comprise an adjuvant to enhance immunogenicity such as alum adjuvant or other adjuvants approved for human use.

[0048] Compositions of the present may be administered as a chemotherapeutic agent to a subject infected with a malaria parasite to prevent or decrease clinical severity of the infection. Alternatively, compositions of the present invention may be administered as immunologic agents to prevent or inhibit infection in subjects at risk for infection by a malaria parasite.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 16

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<211> LENGTH: 498
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum strain 3D7

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Leu Ser Asp Val Lys Gly Ile Ser Thr His Asp Thr Cys Asp Glu Trp
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Ser Glu Trp Ser Ala Cys Thr His Gly Ile Ser Thr Arg Lys Cys Leu
35                  40                  45

Ser Asp Ser Ser Ile Lys Asp Glu Thr Leu Val Cys Thr Lys Cys Asp
50                  55                  60

Lys Trp Gly Glu Trp Ser Glu Cys Lys Asp Gly Arg Met His Arg Lys
65                  70                  75                  80

Val Leu Asn Cys Pro Phe Ile Lys Glu Glu Gln Glu Cys Asp Val Asn
85                  90                  95

Asn Glu Met Ala Glu Asp Thr His Met Asn Asn Ser Tyr Ile Tyr Phe
100                 105                 110

Asn Ala Asp Asp Gly Asp Asn Glu Tyr Glu Asp His Asp Asp Lys Asn
115                 120                 125

Asp Asp Asp Lys Asn Tyr Asp Asn Glu Asn Asp Asp Asp Lys Asn Asp
130                 135                 140

Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp
145                 150                 155                 160

Asp Lys Asn Asp Asp Glu Glu Asn Tyr Asn Asp Thr Glu Glu Lys Val
165                 170                 175

Lys Asn Asn Asp Ile His Asn Ser Ser Ala Asn Ser Asn Asn Glu Val
180                 185                 190

Thr Asn Phe Ile Gln Ile Lys Asp Lys Ile Met Ile Lys His Lys Thr
195                 200                 205

Thr Asn Ile His Pro Val Asn Phe Ile Gln Glu Lys Tyr Thr Arg Asn
210                 215                 220
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Asn Lys Tyr Arg Ser Asp Asn Phe Ser Lys Ile Leu Asn Asn Met Asn
225                 230                 235                 240

His Ile Asn Asn Asn Asn Tyr Asn Ser Arg Ser Ser Ser Thr Ser Ser
245                 250                 255

Lys Asn Ala Arg Gly Tyr Arg Gly Gly Ser Ser Asn Met Tyr Pro His
260                 265                 270

Val Pro Asn Tyr Thr Ser Ser Ser Val His Asn Ser Thr Asn Asn Glu
275                 280                 285

Arg Lys Ser Asp Glu Asp Leu Asp Asn Ile Glu Gly Asp Asn Ile Thr
290                 295                 300

Lys Glu Glu Arg Ile Val Pro Ile Asn Asn Lys Asn Tyr Asp Asn His
305                 310                 315                 320

Asp Glu His Ser Asn Ile His Glu His Asp Thr Ser Arg Asn Val Asp
325                 330                 335

Asn Glu Lys Tyr Asn Ser Asn Asp Asp Leu Pro Asn Leu Ser Thr Tyr
340                 345                 350

Asp Tyr Asp Met Asn Asn Asp Ser Tyr Lys Lys Asn His Met Lys Lys
355                 360                 365

Pro Met Asp Ser Ile Lys Glu Glu Gln Thr Lys Gln Glu Asn Asn Gln
370                 375                 380

Asn Asn Glu Lys Val Ser Ser Ser Glu Lys Gln Asn Asp Asp Ile Ser
385                 390                 395                 400

Ala Leu Tyr Glu His Met Asn Thr Lys Asp Gln Glu His Thr Gln His
405                 410                 415

Glu Gln Pro Asn Asp Ser Ala His Gly His Phe Glu Asp Tyr Ser Lys
420                 425                 430

Leu Tyr Ile Ala Ser Gly Val Ala Thr Leu Val Leu Leu Gly Gly Ser
435                 440                 445

Ile Thr Phe Tyr Phe Leu Arg Lys Glu Lys Thr Glu Lys Val Val Gln
450                 455                 460

Glu Glu Thr Lys Glu Glu Asn Phe Glu Val Met Phe Asn Asp Asp Ala
465                 470                 475                 480

Leu Lys Gly Lys Asp Asn Lys Ala Met Asp Glu Glu Glu Phe Trp Ala
485                 490                 495

Leu Glu
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<210> SEQ ID NO 2
<211> LENGTH: 1497
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum strain 3D7

<400> SEQUENCE: 2

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ggaatcagta ccaggaaatg tttaagtgat tcttctatta aggatgagac acttgtatgt    180

acaaaatgtg ataaatgggg agaatggtca gaatgtaaag atgggagaat gcatagaaaa    240

gttttgaatt gtccttttat taaagaagaa caagaatgtg atgtaaataa tgaaatggcg    300

gaggacacac atatgaataa tagctatata tatttcaacg cagatgatgg tgataatgaa    360

tatgaagatc atgatgataa aaatgatgat gataaaaatt atgataatga aaatgatgat    420

gataaaaatg atgatgataa aaatgatgat gataaaaatg atgatgataa aaatgatgat    480
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atacataatt ctagtgctaa tagtaataat gaggttacta atttcataca gataaaagat 600

aaaattatga ttaaacataa aacaacaaat atacatccag tgaattttat acaagaaaaa 660

tatacaagaa ataataaata tagatctgat aatttttcta aaatattaaa taacatgaat 720

catataaata ataataatta taatagtaga agtagtagta cttcttcgaa aaatgctaga 780

ggttatagag gaggaagcag taatatgtat ccacatgtac caaattacac gagttcttct 840

gtacataata gtacaaataa tgaaagaaaa agtgatgaag acttggataa tatagagggt 900

gataatataa ctaaagaaga aaggattgtt ccaataaata acaaaaatta tgataatcat 960

gatgaacata gtaatataca cgagcatgat acatctcgta atgtagataa tgaaaaatat 1020

aattcaaatg atgatttacc aaacttgtcg acttatgatt atgatatgaa taatgattct 1080

tataaaaaga atcacatgaa aaaacctatg gattctatta aagaagaaca aacaaaacaa 1140

gaaaataatc agaacaatga aaaagtatcc tcctcagaaa aacaaaatga tgatatatct 1200

gcattatatg aacatatgaa taccaaggat caagagcata cacaacatga acaaccaaat 1260

gacagtgcac atggtcactt tgaagattac agtaaattat atattgctag tggtgtagct 1320

actcttgtac tcttgggagg aagtataact ttctatttct tacgtaaaga aaaaacagaa 1380

aaagttgtac aagaagaaac aaaagaggaa aactttgaag tcatgtttaa tgatgatgct 1440

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<211> LENGTH: 488
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum strain FVO

<400> SEQUENCE: 3

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1 5 10 15

Leu Ser Asp Val Lys Gly Ile Ser Thr His Asp Thr Cys Asp Glu Trp
20 25 30

Ser Glu Trp Ser Ala Cys Thr His Gly Ile Ser Thr Arg Lys Cys Leu
35 40 45

Ser Asp Ser Ser Ile Lys Asp Glu Thr Leu Val Cys Thr Lys Cys Asp
50 55 60

Lys Trp Gly Glu Trp Ser Glu Cys Lys Asp Gly Arg Met His Arg Lys
65 70 75 80

Val Leu Asn Cys Pro Phe Ile Lys Glu Glu Gln Glu Cys Asp Val Asn
85 90 95

Asn Glu Met Ala Glu Asp Thr His Met Asn Asn Ser Tyr Ile Tyr Phe
100 105 110

Asn Ala Asp Asp Gly Asp Asn Glu Tyr Glu Asp His Asp Asp Lys Asn
115 120 125

Asp Asp Asp Lys Asn Tyr Asp Asn Glu Asn Asp Asp Asp Lys Asn Asp
130 135 140

Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp Glu Glu Asn Tyr Asn
145 150 155 160

Asp Thr Glu Glu Lys Val Lys Asn Asn Asp Ile His Asn Ser Ser Ala
165 170 175

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Asn Ser Asn Asn Glu Val Thr Asn Phe Ile Gln Ile Lys Asp Lys Ile
180                 185                 190

Met Ile Lys His Lys Thr Thr Asn Ile His Pro Val Asn Phe Ile Gln
195                 200                 205

Glu Lys Tyr Thr Arg Asn Asn Lys Tyr Arg Ser Asp Asn Phe Ser Lys
210                 215                 220

Ile Leu Asn Asn Met Asn His Ile Asn Asn Asn Asn Tyr Asn Ser Arg
225                 230                 235                 240

Ser Ser Ser Thr Ser Ser Lys Asn Ala Arg Gly Tyr Arg Gly Gly Ser
245                 250                 255

Ser Asn Met Tyr Pro His Val Pro Asn Tyr Thr Ser Ser Ser Val His
260                 265                 270

Asn Ser Thr Asn Asn Glu Arg Lys Ser Asp Glu Asp Leu Asp Asn Ile
275                 280                 285

Glu Gly Asp Asn Ile Thr Lys Glu Glu Arg Ile Val Pro Ile Asn Asn
290                 295                 300

Lys Asn Tyr Asp Asn His Asp Glu His Ser Asn Ile His Glu His Asp
305                 310                 315                 320

Thr Ser Arg Asn Val Asp Asn Glu Lys Tyr Asn Ser Asn Asp Asp Leu
325                 330                 335

Pro Asn Leu Ser Thr Tyr Asp Tyr Asp Met Asn Asn Asp Ser Tyr Lys
340                 345                 350

Lys Asn His Met Lys Lys Pro Met Asp Ser Ile Lys Glu Glu Gln Thr
355                 360                 365

Lys Gln Glu Asn Asn Gln Asn Asn Glu Lys Val Ser Ser Ser Glu Lys
370                 375                 380

Gln Asn Asp Asp Ile Ser Ala Leu Tyr Glu His Met Asn Thr Lys Asp
385                 390                 395                 400

Gln Glu His Thr Gln His Glu Gln Thr Asn Asp Ser Ala His Gly His
405                 410                 415

Phe Glu Asp Tyr Ser Lys Leu Tyr Ile Ala Ser Gly Val Ala Thr Leu
420                 425                 430

Val Leu Leu Gly Gly Ser Ile Thr Phe Tyr Phe Leu Arg Lys Glu Lys
435                 440                 445

Thr Glu Lys Val Val Gln Glu Glu Thr Lys Glu Glu Asn Phe Glu Val
450                 455                 460

Met Phe Asn Asp Asp Ala Leu Lys Gly Lys Asp Asn Lys Ala Met Asp
465                 470                 475                 480

Glu Glu Glu Phe Trp Ala Leu Glu
485
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<210> SEQ ID NO 4
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<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum strain FVO

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ggaatcagta ccaggaaatg tttaagtgat tcttctatta aggatgagac acttgtatgt    180

acaaaatgtg ataaatgggg agaatggtca gaatgtaaag atgggagaat gcatagaaaa    240
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gaggacacac atatgaataa tagctatata tatttcaacg cagatgatgg tgataatgaa 360

tatgaagatc atgatgataa aaatgatgat gataaaaatt atgataatga aaatgatgat 420

gataaaaatg atgatgataa aaatgatgat gataaaaatg atgatgagga aaattataat 480

gatactgaag aaaaggtaaa aaataatgat atacataatt ctagtgctaa tagtaataat 540

gaggttacta atttcataca gataaaagat aaaattatga ttaaacataa aacaacaaat 600

atacatccag tgaattttat acaagaaaaa tatacaagaa ataataaata tagatctgat 660

aatttttcta aaatattaaa taacatgaat catataaata ataataatta taatagtaga 720

agtagtagta cttcttcgaa aaatgctaga ggttatagag gaggaagcag taatatgtat 780

ccacatgtac caaattacac gagttcttct gtacataata gtacaaataa tgaaagaaaa 840

agtgatgaag acttggataa tatagagggt gataatataa ctaaagaaga aaggattgtt 900

ccaataaata acaaaaatta tgataatcat gatgaacata gtaatataca cgagcatgat 960

acatctcgta atgtagataa tgaaaaatat aattcaaatg atgatttacc aaacttgtcg 1020

acttatgatt atgatatgaa taatgattct tataaaaaga atcacatgaa aaaacctatg 1080

gattctatta aagaagaaca aacaaaacaa gaaaataatc agaacaatga aaaagtatcc 1140

tcctcagaaa aacaaaatga tgatatatct gcattatatg aacatatgaa taccaaggat 1200

caagagcata cacaacatga acaaacaaat gacagtgcac atggtcactt tgaagattac 1260

agtaaattat atattgctag tggtgtagct actcttgtac tcttgggagg aagtataact 1320

ttctatttct tacgtaaaga aaaaacagaa aaagttgtac aagaagaaac aaaagaggaa 1380

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gaagaagaat tctgggcact cgaatga 1467

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Leu Ser Asp Val Lys Gly Ile Ser Thr His Asp Thr Cys Asp Glu Trp
20 25 30

Ser Glu Trp Ser Ala Cys Thr His Gly Ile Ser Thr Arg Lys Cys Leu
35 40 45

Ser Asp Ser Ser Ile Lys Asp Glu Thr Leu Val Cys Thr Lys Cys Asp
50 55 60

Lys Trp Gly Glu Trp Ser Glu Cys Lys Asp Gly Arg Met His Arg Lys
65 70 75 80

Val Leu Asn Cys Pro Phe Ile Lys Glu Glu Gln Glu Cys Asp Val Asn
85 90 95

Asn Glu Met Ala Glu Asp Thr His Met Asn Asn Ser Tyr Ile Tyr Phe
100 105 110

Asn Ala Asp Asp Gly Asp Asn Glu Tyr Glu Asp His Asp Asp Lys Asn
115 120 125

Asp Asp Asp Lys Asn Tyr Asp Asn Glu Asn Asp Asp Asp Lys Tyr Asp
130 135 140

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Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp
145                 150                 155                 160

Glu Glu Asn Tyr Asn Asp Thr Glu Glu Lys Val Lys Asn Asn Asp Ile
165                 170                 175

His Asn Ser Ser Ala Asn Ser Asn Asn Glu Val Thr Asn Phe Ile Gln
180                 185                 190

Ile Lys Asp Lys Ile Met Ile Lys His Lys Thr Thr Asn Ile His Pro
195                 200                 205

Val Asn Phe Ile Gln Glu Lys Tyr Thr Arg Asn Asn Lys His Arg Ser
210                 215                 220

Asp Asn Phe Ser Lys Ile Leu Asn Asn Met Asn His Ile Asn Asn Asn
225                 230                 235                 240

Asn Tyr Asn Ser Arg Ser Ser Ser Thr Ser Ser Lys Asn Ala Arg Gly
245                 250                 255

Tyr Arg Gly Gly Ser Ser Asn Met Tyr Pro His Val Pro Asn Tyr Thr
260                 265                 270

Ser Ser Ser Val His Asn Ser Thr Asn Asn Glu Arg Lys Ser Asp Glu
275                 280                 285

Asp Leu Asp Asn Ile Glu Gly Asp Asn Ile Thr Lys Glu Glu Arg Ile
290                 295                 300

Val Pro Ile Asn Asn Lys Asn Tyr Asp Asn His Asp Glu His Ser Asn
305                 310                 315                 320

Ile His Glu His Asp Thr Ser Arg Asn Val Asp Asn Glu Lys Tyr Asn
325                 330                 335

Ser Asn Asp Asp Leu Pro Asn Leu Ser Thr Tyr Asp Tyr Asp Met Asn
340                 345                 350

Asn Asp Ser Tyr Lys Lys Asn His Met Lys Lys Pro Met Asp Ser Ile
355                 360                 365

Lys Glu Glu Gln Thr Lys Gln Glu Asn Asn Gln Asn Asn Glu Lys Val
370                 375                 380

Ser Ser Ser Glu Lys Gln Asn Asp Asp Ile Ser Ala Leu Tyr Glu His
385                 390                 395                 400

Met Asn Thr Lys Asp Gln Glu His Thr Gln His Glu Gln Pro Asn Asp
405                 410                 415

Ser Ala His Gly His Phe Glu Asp Tyr Ser Lys Leu Tyr Ile Ala Ser
420                 425                 430

Gly Val Ala Thr Leu Val Leu Leu Gly Gly Ser Ile Thr Phe Tyr Phe
435                 440                 445

Leu Arg Lys Glu Lys Thr Glu Lys Val Val Gln Glu Glu Thr Lys Glu
450                 455                 460

Glu Asn Phe Glu Val Met Phe Asn Asp Asp Ala Leu Lys Gly Lys Asp
465                 470                 475                 480

Asn Lys Ala Met Asp Glu Glu Glu Phe Trp Ala Leu Glu
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<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum strain D10

<400> SEQUENCE: 6

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acaaaatgtg ataaatgggg agaatggtca gaatgtaaag atgggagaat gcatagaaaa 240

gttttgaatt gtccttttat taaagaagaa caagaatgtg atgtaaataa tgaaatggcg 300

gaggacacac atatgaataa tagctatata tatttcaacg cagatgatgg tgataatgaa 360

tatgaagatc atgatgataa aaatgatgat gataaaaatt atgataatga aaatgatgat 420

gataaatatg atgatgataa aaatgatgat gataaaaatg atgatgataa aaatgatgat 480

gaggaaaatt ataatgatac tgaagaaaag gtaaaaaata atgatataca taattctagt 540

gctaatagta ataatgaggt tactaatttc atacagataa aagataaaat tatgattaaa 600

cataaaacaa caaatataca tccagtgaat tttatacaag aaaaatatac aagaaataat 660

aaacatagat ctgataattt ttctaaaata ttaaataaca tgaatcatat aaataataat 720

aattataata gtagaagtag tagtacttct tcgaaaaatg ctagaggtta tagaggagga 780

agcagtaata tgtatccaca tgtaccaaat tacacgagtt cttctgtaca taatagtaca 840

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ttaccaaact tgtcgactta tgattatgat atgaataatg attcttataa aaagaatcac 1080

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aatgaaaaag tatcctcctc agaaaaacaa aatgatgata tatctgcatt atatgaacat 1200

atgaatacca aggatcaaga gcatacacaa catgaacaac caaatgacag tgcacatggt 1260

cactttgaag attacagtaa attatatatt gctagtggtg tagctactct tgtactcttg 1320

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<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum strain HB3

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Ser Glu Trp Ser Ala Cys Thr His Gly Ile Ser Thr Arg Lys Cys Leu
35 40 45

Ser Asp Ser Ser Ile Lys Asp Glu Thr Leu Val Cys Thr Lys Cys Asp
50 55 60

Lys Trp Gly Glu Trp Ser Glu Cys Lys Asp Gly Arg Met His Arg Lys
65 70 75 80

Val Leu Asn Cys Pro Phe Ile Lys Glu Glu Gln Glu Cys Asp Val Asn
85 90 95

Asn Glu Met Ala Glu Asp Thr His Met Asn Asn Ser Tyr Ile Tyr Phe

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100                 105                 110

Asn Ala Asp Asp Gly Asp Asn Glu Tyr Glu Asp His Asp Asp Lys Asn
115                 120                 125

Asp Asp Asp Lys Asn Tyr Asp Asn Glu Asn Asp Asp Asp Lys Asn Asp
130                 135                 140

Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp
145                 150                 155                 160

Asp Lys Asn Asp Asp Glu Glu Asn Tyr Asn Asp Thr Glu Glu Lys Val
165                 170                 175

Lys Asn Asn Asp Ile His Asn Ser Ser Ala Asn Ser Asn Asn Glu Val
180                 185                 190

Thr Asn Phe Ile Gln Ile Lys Asp Lys Ile Met Ile Lys His Lys Thr
195                 200                 205

Thr Asn Ile His Pro Val Asn Phe Ile Gln Glu Lys Tyr Thr Arg Asn
210                 215                 220

Asn Lys Tyr Arg Ser Asp Asn Phe Ser Lys Ile Leu Asn Asn Met Asn
225                 230                 235                 240

His Ile Asn Asn Asn Asn Tyr Asn Ser Arg Ser Ser Ser Thr Ser Ser
245                 250                 255

Lys Asn Ala Arg Gly Tyr Arg Gly Gly Ser Ser Asn Met Tyr Pro His
260                 265                 270

Val Pro Asn Tyr Thr Ser Ser Ser Val His Asn Ser Thr Asn Asn Glu
275                 280                 285

Arg Lys Ser Asp Glu Asp Leu Asp Asn Ile Glu Gly Asp Asn Ile Thr
290                 295                 300

Lys Glu Glu Arg Ile Val Pro Ile Asn Asn Lys Asn Tyr Asp Asn His
305                 310                 315                 320

Asp Glu His Ser Asn Ile His Glu His Asp Thr Ser Arg Asn Val Asp
325                 330                 335

Asn Glu Lys Tyr Asn Ser Asn Asp Asp Leu Pro Asn Leu Ser Thr Tyr
340                 345                 350

Asp Tyr Asp Met Asn Asn Asp Ser Tyr Lys Lys Asn His Met Lys Lys
355                 360                 365

Pro Met Asp Ser Ile Lys Glu Glu Gln Thr Lys Gln Glu Asn Asn Gln
370                 375                 380

Asn Asn Glu Lys Val Ser Ser Ser Glu Lys Gln Asn Asp Asp Ile Ser
385                 390                 395                 400

Ala Leu Tyr Glu His Met Asn Thr Lys Asp Gln Glu His Thr Gln His
405                 410                 415

Glu Gln Pro Asn Asp Ser Ala His Gly His Phe Glu Asp Tyr Ser Lys
420                 425                 430

Leu Tyr Ile Ala Ser Gly Val Ala Thr Leu Val Leu Leu Gly Gly Ser
435                 440                 445

Ile Thr Phe Tyr Phe Leu Arg Lys Glu Lys Thr Glu Lys Val Val Gln
450                 455                 460

Glu Glu Thr Lys Glu Glu Asn Phe Glu Val Met Phe Asn Asp Asp Ala
465                 470                 475                 480

Leu Lys Gly Lys Asp Asn Lys Ala Met Asp Glu Glu Glu Phe Trp Ala
485                 490                 495

Leu Glu
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<210> SEQ ID NO 8
<211> LENGTH: 1497
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum strain HB3

<400> SEQUENCE: 8

atgaagaaaa caatcctaaa tttatatttg ataaatatat tatttgcctt atctgacgta 60

aaaggtatat caacacatga tacatgcgat gaatggtcag aatggtctgc atgtactcat 120

ggaatcagta ccaggaaatg tttaagtgat tcttctatta aggatgagac acttgtatgt 180

acaaaatgtg ataaatgggg agaatggtca gaatgtaaag atgggagaat gcatagaaaa 240

gttttgaatt gtccttttat taaagaagaa caagaatgtg atgtaaataa tgaaatggcg 300

gaggacacac atatgaataa tagctatata tatttcaacg cagatgatgg tgataatgaa 360

tatgaagatc atgatgataa aaatgatgat gataaaaatt atgataatga aaatgatgat 420

gataaaaatg atgatgataa aaatgatgat gataaaaatg atgatgataa aaatgatgat 480

gataaaaatg atgatgagga aaattataat gatactgaag aaaaggtaaa aaataatgat 540

atacataatt ctagtgctaa tagtaataat gaggttacta atttcataca gataaaagat 600

aaaattatga ttaaacataa aacaacaaat atacatccag tgaattttat acaagaaaaa 660

tatacaagaa ataataaata tagatctgat aatttttcta aaatattaaa taacatgaat 720

catataaata ataataatta taatagtaga agtagtagta cttcttcgaa aaatgctaga 780

ggttatagag gaggaagcag taatatgtat ccacatgtac caaattacac gagttcttct 840

gtacataata gtacaaataa tgaaagaaaa agtgatgaag acttggataa tatagagggt 900

gataatataa ctaaagaaga aaggattgtt ccaataaata acaaaaatta tgataatcat 960

gatgaacata gtaatataca cgagcatgat acatctcgta atgtagataa tgaaaaatat 1020

aattcaaatg atgatttacc aaacttgtcg acttatgatt atgatatgaa taatgattct 1080

tataaaaaga atcacatgaa aaaacctatg gattctatta aagaagaaca aacaaaacaa 1140

gaaaataatc agaacaatga aaaagtatcc tcctcagaaa aacaaaatga tgatatatct 1200

gcattatatg aacatatgaa taccaaggat caagagcata cacaacatga acaaacaaat 1260

gacagtgcac atggtcactt tgaagattac agtaaattat atattgctag tggtgtagct 1320

actcttgtac tcttgggagg aagtataact ttctatttct tacgtaaaga aaaaacagaa 1380

aaagttgtac aagaagaaac aaaagaggaa aactttgaag tcatgtttaa tgatgatgct 1440

ctcaagggaa aggataacaa agctatggat gaagaagaat tctgggcact cgaatga 1497

<210> SEQ ID NO 9
<211> LENGTH: 498
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum strain M24

<400> SEQUENCE: 9

Met Lys Lys Thr Ile Leu Asn Leu Tyr Leu Ile Asn Ile Leu Phe Ala
1 5 10 15

Leu Ser Asp Val Lys Gly Ile Ser Thr His Asp Thr Cys Asp Glu Trp
20 25 30

Ser Glu Trp Ser Ala Cys Thr His Gly Ile Ser Thr Arg Lys Cys Leu
35 40 45

Ser Asp Ser Ser Ile Lys Asp Glu Thr Leu Val Cys Thr Lys Cys Asp

-continued

```
50                  55                  60

Lys Trp Gly Glu Trp Ser Glu Cys Lys Asp Gly Arg Met His Arg Lys
65                  70                  75                  80

Val Leu Asn Cys Pro Phe Ile Lys Glu Glu Gln Glu Cys Asp Val Asn
85                  90                  95

Asn Glu Met Ala Glu Asp Thr His Met Asn Asn Ser Tyr Ile Tyr Phe
100                 105                 110

Asn Ala Asp Asp Gly Asp Asn Glu Tyr Glu Asp His Asp Asp Lys Asn
115                 120                 125

Asp Asp Asp Lys Asn Tyr Asp Asn Glu Asn Asp Asp Asp Lys Asn Asp
130                 135                 140

Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp
145                 150                 155                 160

Asp Lys Asn Asp Asp Glu Glu Asn Tyr Asn Asp Thr Glu Glu Lys Val
165                 170                 175

Lys Asn Asn Asp Ile His Asn Ser Ser Ala Asn Ser Asn Asn Glu Val
180                 185                 190

Thr Asn Phe Ile Gln Ile Lys Asp Lys Ile Met Ile Lys His Lys Thr
195                 200                 205

Thr Asn Ile His Pro Val Asn Phe Ile Gln Glu Lys Tyr Thr Arg Asn
210                 215                 220

Asn Lys Tyr Arg Ser Asp Asn Phe Ser Lys Ile Leu Asn Asn Met Asn
225                 230                 235                 240

His Ile Asn Asn Asn Asn Tyr Asn Ser Arg Ser Ser Ser Thr Ser Ser
245                 250                 255

Lys Asn Ala Arg Gly Tyr Arg Gly Gly Ser Ser Asn Met Tyr Pro His
260                 265                 270

Val Pro Asn Tyr Thr Ser Ser Ser Val His Asn Ser Thr Asn Asn Glu
275                 280                 285

Arg Lys Ser Asp Glu Asp Leu Asp Asn Ile Glu Gly Asp Asn Ile Thr
290                 295                 300

Lys Glu Glu Arg Ile Val Pro Ile Asn Asn Lys Asn Tyr Asp Asn His
305                 310                 315                 320

Asp Glu His Ser Asn Ile His Glu His Asp Thr Ser Arg Asn Val Asp
325                 330                 335

Asn Glu Lys Tyr Asn Ser Asn Asp Asp Leu Pro Asn Leu Ser Thr Tyr
340                 345                 350

Asp Tyr Asp Met Asn Asn Asp Ser Tyr Lys Lys Asn His Met Lys Lys
355                 360                 365

Pro Met Asp Ser Ile Lys Glu Glu Gln Thr Lys Gln Glu Asn Asn Gln
370                 375                 380

Asn Asn Glu Lys Val Ser Ser Ser Glu Lys Gln Asn Asp Asp Ile Ser
385                 390                 395                 400

Ala Leu Tyr Glu His Met Asn Thr Lys Asp Gln Glu His Thr Gln His
405                 410                 415

Glu Gln Pro Asn Asp Ser Ala His Gly His Phe Glu Asp Tyr Ser Lys
420                 425                 430

Leu Tyr Ile Ala Ser Gly Val Ala Thr Leu Val Leu Leu Gly Gly Ser
435                 440                 445

Ile Thr Phe Tyr Phe Leu Arg Lys Glu Lys Thr Glu Lys Val Val Gln
450                 455                 460
```

-continued

Glu Glu Thr Lys Glu Glu Asn Phe Glu Val Met Phe Asn Asp Asp Ala
465 470 475 480

Leu Lys Gly Lys Asp Asn Lys Ala Met Asp Glu Glu Glu Phe Trp Ala
485 490 495

Leu Glu

<210> SEQ ID NO 10
<211> LENGTH: 1497
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum strain M24

<400> SEQUENCE: 10

atgaagaaaa caatactaaa tttatatttg ataaatatat tatttgcctt atctgacgta 60

aaaggtatat caacacatga tacatgcgat gaatggtcag aatggtctgc atgtactcat 120

ggaatcagta ccaggaaatg tttaagtgat tcttctatta aggatgagac acttgtatgt 180

acaaaatgtg ataaatgggg agaatggtca gaatgtaaag atgggagaat gcatagaaaa 240

gttttgaatt gtccttttat taaagaagaa caagaatgtg atgtaaataa tgaaatggcg 300

gaggacacac atatgaataa tagctatata tatttcaacg cagatgatgg tgataatgaa 360

tatgaagatc atgatgataa aaatgatgat gataaaaatt atgataatga aaatgatgat 420

gataaaaatg atgatgataa aaatgatgat gataaaaatg atgatgataa aaatgatgat 480

gataaaaatg atgatgagga aaattataat gatactgaag aaaaggtaaa aaataatgat 540

atacataatt ctagtgctaa tagtaataat gaggttacta atttcataca gataaaagat 600

aaaattatga ttaaacataa aacaacaaat atacatccag tgaattttat acaagaaaaa 660

tatacaagaa ataataaata tagatctgat aatttttcta aaatattaaa taacatgaat 720

catataaata ataataatta taatagtaga agtagtagta cttcttcgaa aaatgctaga 780

ggttatagag gaggaagcag taatatgtat ccacatgtac caaattacac gagttcttct 840

gtacataata gtacaaataa tgaaagaaaa agtgatgaag acttggataa tatagagggt 900

gataatataa ctaaagaaga aaggattgtt ccaataaata acaaaaatta tgataatcat 960

gatgaacata gtaatataca cgagcatgat acatctcgta atgtagataa tgaaaaatat 1020

aattcaaatg atgatttacc aaacttgtcg acttatgatt atgatatgaa taatgattct 1080

tataaaaaga atcacatgaa aaaacctatg gattctatta aagaagaaca aacaaaacaa 1140

gaaaataatc agaacaatga aaaagtatcc tcctcagaaa aacaaaatga tgatatatct 1200

gcattatatg aacatatgaa taccaaggat caagagcata cacaacatga acaaccaaat 1260

gacagtgcac atggtcactt tgaagattac agtaaattat atattgctag tggtgtagct 1320

actcttgtac tcttgggagg aagtataact ttctatttct tacgtaaaga aaaaacagaa 1380

aaagttgtac aagaagaaac aaaagaggaa aactttgaag tcatgtttaa tgatgatgct 1440

ctcaagggaa aggataacaa agctatggat gaagaagaat tctgggcact cgaatga 1497

<210> SEQ ID NO 11
<211> LENGTH: 503
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum strain MCAMP

<400> SEQUENCE: 11

Met Lys Lys Thr Ile Leu Asn Leu Tyr Leu Ile Asn Ile Leu Phe Ala

-continued

```
1               5                   10                  15

Leu Ser Asp Val Lys Gly Ile Ser Thr His Asp Thr Cys Asp Glu Trp
20                  25                  30

Ser Glu Trp Ser Ala Cys Thr His Gly Ile Ser Thr Arg Lys Cys Leu
35                  40                  45

Ser Asp Ser Ser Ile Lys Asp Glu Thr Leu Val Cys Thr Lys Cys Asp
50                  55                  60

Lys Trp Gly Glu Trp Ser Glu Cys Lys Asp Gly Arg Met His Arg Lys
65                  70                  75                  80

Val Leu Asn Cys Pro Phe Ile Lys Glu Glu Gln Glu Cys Asp Val Asn
85                  90                  95

Asn Glu Met Ala Glu Asp Thr His Met Asn Asn Ser Tyr Ile Tyr Phe
100                 105                 110

Asn Ala Asp Asp Gly Asp Asn Glu Tyr Glu Asp His Asp Asp Lys Asn
115                 120                 125

Asp Asp Asp Lys Asn Tyr Asp Asn Glu Asn Asp Asp Asp Lys Asn Asp
130                 135                 140

Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp
145                 150                 155                 160

Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp Glu Glu Asn Tyr Asn Asp
165                 170                 175

Thr Glu Glu Lys Val Lys Asn Asn Asp Ile His Asn Ser Ser Ala Asn
180                 185                 190

Ser Asn Asn Glu Val Thr Asn Phe Ile Gln Ile Lys Asp Lys Ile Met
195                 200                 205

Ile Lys His Lys Thr Thr Asn Ile His Pro Val Asn Phe Ile Gln Glu
210                 215                 220

Lys Tyr Thr Arg Asn Asn Lys Tyr Arg Ser Asp Asn Phe Ser Lys Ile
225                 230                 235                 240

Leu Asn Asn Met Asn His Ile Asn Asn Asn Asn Tyr Asn Ser Arg Ser
245                 250                 255

Ser Ser Thr Ser Ser Lys Asn Ala Arg Gly Tyr Arg Gly Gly Ser Ser
260                 265                 270

Asn Met Tyr Pro His Val Pro Asn Tyr Thr Ser Ser Ser Val His Asn
275                 280                 285

Ser Thr Asn Asn Glu Arg Lys Ser Asp Glu Asp Leu Asp Asn Ile Glu
290                 295                 300

Gly Asp Asn Ile Thr Lys Glu Glu Arg Ile Val Pro Ile Asn Asn Lys
305                 310                 315                 320

Asn Tyr Asp Asn His Asp Glu His Ser Asn Ile His Glu His Asp Thr
325                 330                 335

Ser Arg Asn Val Asp Asn Glu Lys Tyr Asn Ser Asn Asp Asp Leu Pro
340                 345                 350

Asn Leu Ser Thr Tyr Asp Tyr Asp Met Asn Asn Asp Ser Tyr Lys Lys
355                 360                 365

Asn His Met Lys Lys Pro Met Asp Ser Ile Lys Glu Glu Gln Thr Lys
370                 375                 380

Gln Glu Asn Asn Gln Asn Asn Glu Lys Val Ser Ser Ser Glu Lys Gln
385                 390                 395                 400

Asn Asp Asp Ile Ser Ala Leu Tyr Glu His Met Asn Thr Lys Asp Gln
405                 410                 415
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-continued

Glu His Thr Gln His Glu Gln Thr Asn Asp Ser Ala His Gly His Phe
420 425 430

Glu Asp Tyr Ser Lys Leu Tyr Ile Ala Ser Gly Val Ala Thr Leu Val
435 440 445

Leu Leu Gly Gly Ser Ile Thr Phe Tyr Phe Leu Arg Lys Glu Lys Thr
450 455 460

Glu Lys Val Val Gln Glu Glu Thr Lys Glu Glu Asn Phe Glu Val Met
465 470 475 480

Phe Asn Asp Asp Ala Leu Lys Gly Lys Asp Asn Lys Ala Met Asp Glu
485 490 495

Glu Glu Phe Trp Ala Leu Glu
500

<210> SEQ ID NO 12
<211> LENGTH: 1512
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum strain MCAMP

<400> SEQUENCE: 12

atgaagaaaa caatactaaa tttatatttg ataaatatat tatttgcctt atctgacgta 60

aaaggtatat caacacatga tacatgcgat gaatggtcag aatggtctgc atgtactcat 120

ggaatcagta ccaggaaatg tttaagtgat tcttctatta aggatgagac acttgtatgt 180

acaaaatgtg ataaatgggg agaatggtca gaatgtaaag atgggagaat gcatagaaaa 240

gttttgaatt gtccttttat taaagaagaa caagaatgtg atgtaaataa tgaaatggcg 300

gaggacacac atatgaataa tagctatata tatttcaacg cagatgatgg tgataatgaa 360

tatgaagatc atgatgataa aaatgatgat gataaaaatt atgataatga aaatgatgat 420

gataaaaatg atgatgataa aaatgatgat gataaaaatg atgatgataa aaatgatgat 480

gataaaaatg atgatgataa aaatgatgat gaggaaaatt ataatgatac tgaagaaaag 540

gtaaaaaata atgatataca taattctagt gctaatagta ataatgaggt tactaatttc 600

atacagataa aagataaaat tatgattaaa cataaaacaa caaatataca tccagtgaat 660

tttatacaag aaaaatatac aagaaataat aaatatagat ctgataattt ttctaaaata 720

ttaaataaca tgaatcatat aaataataat aattataata gtagaagtag tagtacttct 780

tcgaaaaatg ctagaggtta tagaggagga agcagtaata tgtatccaca tgtaccaaat 840

tacacgagtt cttctgtaca taatagtaca aataatgaaa gaaaaagtga tgaagacttg 900

gataatatag agggtgataa tataactaaa gaagaaagga ttgttccaat aaataacaaa 960

aattatgata atcatgatga acatagtaat atacacgagc atgatacatc tcgtaatgta 1020

gataatgaaa aatataattc aaatgatgat ttaccaaact tgtcgactta tgattatgat 1080

atgaataatg attcttataa aaagaatcac atgaaaaaac ctatggattc tattaaagaa 1140

gaacaaacaa aacaagaaaa taatcagaac aatgaaaaag tatcctcctc agaaaaacaa 1200

aatgatgata tatctgcatt atatgaacat atgaatacca aggatcaaga gcatacacaa 1260

catgaacaac caaatgacag tgcacatggt cactttgaag attacagtaa attatatatt 1320

gctagtggtg tagctactct tgtactcttg ggaggaagta taactttcta tttcttacgt 1380

aaagaaaaaa cagaaaaagt tgtacaagaa gaaacaaaag aggaaaactt tgaagtcatg 1440

tttaatgatg atgctctcaa gggaaaggat aacaaagcta tggatgaaga agaattctgg 1500

-continued

gcactcgaat ga 1512

<210> SEQ ID NO 13
<211> LENGTH: 488
<212> TYPE: PRT
<213> ORGANISM: Plasmodium falciparum strain C2A

<400> SEQUENCE: 13

Met Lys Lys Thr Ile Leu Asn Leu Tyr Leu Ile Asn Ile Leu Phe Ala
1 5 10 15

Leu Ser Asp Val Lys Gly Ile Ser Thr His Asp Thr Cys Asp Glu Trp
20 25 30

Ser Glu Trp Ser Ala Cys Thr His Gly Ile Ser Thr Arg Lys Cys Leu
35 40 45

Ser Asp Ser Ser Ile Lys Asp Glu Thr Leu Val Cys Thr Lys Cys Asp
50 55 60

Lys Trp Gly Glu Trp Ser Glu Cys Lys Asp Gly Arg Met His Arg Lys
65 70 75 80

Val Leu Asn Cys Pro Phe Ile Lys Glu Glu Gln Glu Cys Asp Val Asn
85 90 95

Asn Glu Met Ala Glu Asp Thr His Met Asn Asn Ser Tyr Ile Tyr Phe
100 105 110

Asn Ala Asp Asp Gly Asp Asn Glu Tyr Glu Asp His Asp Asp Lys Asn
115 120 125

Asp Asp Asp Lys Asn Tyr Asp Asn Glu Asn Asp Asp Asp Lys Asn Asp
130 135 140

Asp Asp Lys Asn Asp Asp Asp Lys Asn Asp Asp Glu Glu Asn Tyr Asn
145 150 155 160

Asp Thr Glu Glu Lys Val Lys Asn Asn Asp Ile His Asn Ser Ser Ala
165 170 175

Asn Ser Asn Asn Glu Val Thr Asn Phe Ile Gln Ile Lys Asp Lys Ile
180 185 190

Met Ile Lys His Lys Thr Thr Asn Ile His Pro Val Asn Phe Ile Gln
195 200 205

Glu Lys Tyr Thr Arg Asn Asn Lys His Arg Ser Asp Asn Phe Ser Lys
210 215 220

Ile Leu Asn Asn Met Asn His Ile Asn Asn Asn Asn Tyr Asn Ser Arg
225 230 235 240

Ser Ser Ser Thr Ser Ser Lys Asn Ala Arg Gly Tyr Arg Gly Gly Ser
245 250 255

Ser Asn Met Tyr Pro His Val Pro Asn Tyr Thr Ser Ser Ser Val His
260 265 270

Asn Ser Thr Asn Asn Glu Arg Lys Ser Asp Glu Asp Leu Asp Asn Ile
275 280 285

Glu Gly Asp Asn Ile Thr Lys Glu Glu Arg Ile Val Pro Ile Asn Asn
290 295 300

Lys Asn Tyr Asp Asn His Asp Glu His Ser Asn Ile His Glu His Asp
305 310 315 320

Thr Ser Arg Asn Val Asp Asn Glu Lys Tyr Asn Ser Asn Asp Asp Leu
325 330 335

Pro Asn Leu Ser Thr Tyr Asp Tyr Asp Met Asn Asn Asp Ser Tyr Lys
340 345 350

-continued

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Lys Asn His Met Lys Lys Pro Met Asp Ser Ile Lys Glu Glu Gln Thr
355                 360                 365

Lys Gln Glu Asn Asn Gln Asn Asn Glu Lys Val Ser Ser Ser Glu Lys
370                 375                 380

Gln Asn Asp Asp Ile Ser Ala Leu Tyr Glu His Met Asn Thr Lys Asp
385                 390                 395                 400

Gln Glu His Thr Gln His Glu Gln Pro Asn Asp Ser Ala His Gly His
405                 410                 415

Phe Glu Asp Tyr Ser Lys Leu Tyr Ile Ala Ser Gly Val Ala Thr Leu
420                 425                 430

Val Leu Leu Gly Gly Ser Ile Thr Phe Tyr Phe Leu Arg Lys Glu Lys
435                 440                 445

Thr Glu Lys Val Val Gln Glu Glu Thr Lys Glu Glu Asn Phe Glu Val
450                 455                 460

Met Phe Asn Asp Asp Ala Leu Lys Gly Lys Asp Asn Lys Ala Met Asp
465                 470                 475                 480

Glu Glu Glu Phe Trp Ala Leu Glu
485


<210> SEQ ID NO 14
<211> LENGTH: 1467
<212> TYPE: DNA
<213> ORGANISM: Plasmodium falciparum strain C2A

<400> SEQUENCE: 14

atgaagaaaa caatactaaa tttatatttg ataaatatat tatttgcctt atctgacgta     60

aaaggtatat caacacatga tacatgcgat gaatggtcag aatggtctgc atgtactcat    120

ggaatcagta ccaggaaatg tttaagtgat tcttctatta aggatgagac acttgtatgt    180

acaaaatgtg ataaatgggg agaatggtca gaatgtaaag atgggagaat gcatagaaaa    240

gttttgaatt gtccttttat taaagaagaa caagaatgtg atgtaaataa tgaaatggcg    300

gaggacacac atatgaataa tagctatata tatttcaacg cagatgatgg tgataatgaa    360

tatgaagatc atgatgataa aaatgatgat gataaaaatt atgataatga aaatgatgat    420

gataaaaatg atgatgataa aaatgatgat gataaaaatg atgatgagga aaattataat    480

gatactgaag aaaaggtaaa aaataatgat atacataatt ctagtgctaa tagtaataat    540

gaggttacta atttcataca gataaaagat aaaattatga ttaaacataa aacaacaaat    600

atacatccag tgaattttat acaagaaaaa tatacaagaa ataataaaca tagatctgat    660

aatttttcta aaatattaaa taacatgaat catataaata ataataatta taatagtaga    720

agtagtagta cttcttcgaa aaatgctaga ggttatagag gaggaagcag taatatgtat    780

ccacatgtac caaattacac gagttcttct gtacataata gtacaaataa tgaaagaaaa    840

agtgatgaag acttggataa tatagagggt gataatataa ctaaagaaga aaggattgtt    900

ccaataaata acaaaaatta tgataatcat gatgaacata gtaatataca cgagcatgat    960

acatctcgta atgtagataa tgaaaaatat aattcaaatg atgatttacc aaacttgtcg   1020

acttatgatt atgatatgaa taatgattct tataaaaaga atcacatgaa aaaacctatg   1080

gattctatta aagaagaaca aacaaaacaa gaaaataatc agaacaatga aaaagtatcc   1140

tcctcagaaa aacaaaatga tgatatatct gcattatatg aacatatgaa taccaaggat   1200
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-continued

caagagcata cacaacatga acaaacaaat gacagtgcac atggtcactt tgaagattac 1260

agtaaattat atattgctag tggtgtagct actcttgtac tcttgggagg aagtataact 1320

ttctatttct tacgtaaaga aaaaacagaa aaagttgtac aagaagaaac aaaagaggaa 1380

aactttgaag tcatgtttaa tgatgatgct ctcaagggaa aggataacaa agctatggat 1440

gaagaagaat tctgggcact cgaatga 1467

<210> SEQ ID NO 15
<211> LENGTH: 387
<212> TYPE: PRT
<213> ORGANISM: Plasmodium vivax

<400> SEQUENCE: 15

Met Lys Met Ala Ser Phe Lys Ser Leu Leu Leu Asn Ile Phe Phe Phe
1 5 10 15

Ser Leu Ile Gln Ile Ser Cys Lys Arg Ile Gly Lys Arg Lys Cys Glu
20 25 30

Gln Trp Asp Ser Trp Ser Ala Cys Lys Asp Gly Ile Ser Thr Arg Val
35 40 45

Cys Leu Thr Asn Lys Ser Val Thr Asp Lys Met Thr Cys Lys Ala Cys
50 55 60

Asn Ile Trp Gly Asp Trp Ser Ala Cys Lys Asn Gly Lys Arg His Arg
65 70 75 80

Lys Val Val Asn Cys Pro Phe Ile Arg Glu Glu Gln Asp Cys Asp Pro
85 90 95

Asn Lys Ser Asn Lys Gln Asn Ala Arg Asn Asn Thr Thr Ile Tyr Phe
100 105 110

Asn Asn Asp Asp Tyr Asp Asp Glu Gln Asp Asp Val Phe Glu Glu Thr
115 120 125

Leu Gln Glu Glu Ser Asn Leu Pro Val Lys Gly Asp Ser Ser Glu Pro
130 135 140

Ile Phe Leu Glu Gln Asp Ser His Gly Glu Gly Lys Gln Gln Ser Met
145 150 155 160

Ser Glu Ser Phe Ala His Val Asp Glu Val Asp Ala Thr Ala Gln Pro
165 170 175

His Asn Glu Val Leu Thr Asp Thr Thr Thr Pro Ser Glu Ala Ser Pro
180 185 190

Pro Ala Asp Asp Ala Asn Asn Glu Thr Tyr Val Ser Tyr Pro Glu Glu
195 200 205

Glu Pro Leu His Gly Pro Gln Asn Asn Ser Asp Glu Ala Gln Ala Gly
210 215 220

Ala Asp His Leu Ser Ser His Asn Leu Ala Asp Asp Gln Ala Asp Ser
225 230 235 240

Gln Ala Asp Gly Gln Thr Asn Ala Ala Pro Ser Ser Glu Pro Arg Ala
245 250 255

Lys His Phe Arg Asp His Lys Phe Glu Asp Val Ser Ser Pro Pro Gly
260 265 270

Glu Gly Gln Asn Glu Asn His Ala Glu Gly Asn Thr Asn Gln Asn Ser
275 280 285

Phe Tyr Glu Gln Gln Gly Ser His His Glu His Ser Glu His Lys Trp
290 295 300

Arg Lys Lys His Asn Ala Gly Ala Gly Ser Gly Gly Ala Pro Lys Phe

-continued

```
305                 310                 315                 320

Asn Gln Thr Tyr Ile Ala Ser Gly Met Gly Leu Leu Phe Leu Leu Ser
325                 330                 335

Gly Thr Ala Ala Ser Tyr Ala Leu Tyr Asn Gly Lys Tyr Lys Glu Leu
340                 345                 350

Thr Glu Glu Ala Lys Asn Glu Asn Phe Glu Val Ile Phe Asn Glu Asp
355                 360                 365

Met Lys Ala Arg Glu Asn Ser Lys Ser Met Tyr Glu Asp Glu Phe Trp
370                 375                 380

Ala Leu Gly
385
```

<210> SEQ ID NO 16
<211> LENGTH: 375
<212> TYPE: PRT
<213> ORGANISM: Plasmodium knowlesi

<400> SEQUENCE: 16

```
Met Ala Ser Phe Lys Ser Leu Leu Leu Asn Ile Phe Phe Phe Ser Leu
1               5                   10                  15

Ile His Ile Ser Cys Glu Leu Ile Arg Asp Lys Arg Cys Glu Gln Trp
20                  25                  30

Asp Ser Trp Ser Pro Cys Lys Asn Gly Ile Ser Thr Arg Ile Cys Leu
35                  40                  45

Thr Asp Lys Ser Val Thr Asp Lys Met Thr Cys Thr Met Cys Asn Ile
50                  55                  60

Trp Gly Glu Trp Ser Ala Cys Gln Asn Gly Lys Arg His Arg Lys Ile
65                  70                  75                  80

Val Asn Cys Pro Phe Ile Arg Glu Asp Gln Asp Cys Asp Pro Asn Asn
85                  90                  95

Ser Asn Glu Glu Asn Ala Arg Asn Asn Thr Thr Ile Tyr Phe Asn Asn
100                 105                 110

Tyr Asp Asp Glu Gln Gly Asp Asn Phe Glu Glu Thr Leu Glu Glu Glu
115                 120                 125

Ser Asn Leu Pro Val Thr Gly Asp Asn Ser Glu Pro Val Phe Leu Glu
130                 135                 140

Arg Asn Ser His Gly Glu Arg Lys Gln Gln Gly Met Arg Glu Ser Phe
145                 150                 155                 160

Ala His Val Asp Glu Val Asp Thr Thr Ala Gln Glu His Asn Asp Met
165                 170                 175

Leu Thr Asp Thr Thr Pro Ser Glu Ala Ser Pro Pro Ala Asp Asp Ala
180                 185                 190

Ser Glu Asn His Ala Lys Ser Pro Asn Pro Asp Glu Leu Asn Glu Pro
195                 200                 205

His Ile Asn Ser Asp Gly Ala Gln Thr Asp Ala Thr Tyr Asp Pro Ser
210                 215                 220

Ser His Asn Pro Ala Asp Asp Gln Ser Asp Thr Ala Pro Phe Ser Lys
225                 230                 235                 240

Pro Lys Arg Ala Lys Asn Phe Arg Asp His Lys Phe Asp Asp Phe Ser
245                 250                 255

Ser Thr Pro Gly Glu Gly Gln Asn Lys Asn His Ala Glu Gly Asp Thr
260                 265                 270
```

-continued

```
His Arg Gln Ser Phe Lys Glu Gln Gln Gly Asn Gln His Glu Gln Ser
275                 280                 285

Lys Asn Glu Trp Arg Lys Lys His Asn Ala Gly Thr Gly Ser Gly Gly
290                 295                 300

Ala Pro Lys Phe Asn Gln Thr Tyr Ile Ala Ser Gly Met Gly Leu Leu
305                 310                 315                 320

Phe Leu Val Ser Gly Ser Ala Ala Ser Tyr Ala Leu Tyr Asn Gly Lys
325                 330                 335

Tyr Lys Gln Leu Asn Glu Glu Ala Lys Asn Glu Asn Phe Glu Val Ile
340                 345                 350

Phe Asn Glu Asp Met Lys Ala Arg Asp Asn Ser Lys Ser Met Tyr Glu
355                 360                 365

Asp Glu Phe Trp Ala Leu Gly
370                 375
```

1. An isolated protein that interacts with a red blood cell to be invaded by a malaria parasite and links with a component of the actin-myosin based machinery of the malaria parasite.

2. The isolated protein of claim **1** comprising an amino acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11 or 13 or a homolog or ortholog thereof.

3. The isolated protein of claim **2** wherein the ortholog comprises an amino acid sequence of SEQ ID NO:15 or SEQ ID NO:16.

4. An isolated nucleic acid sequence encoding the protein of claim **1**.

5. The isolated nucleic acid sequence of claim **4** comprising a nucleic acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12 or 14.

5. (canceled)

6. A method for identifying potential therapeutic agents for malaria comprising assessing the ability of a potential therapeutic agent to inhibit interaction of the isolated protein of claim **1** with a red blood cell to be invaded by the malaria parasite or to inhibit linkage of the protein of claim **1** to a component of the actin-myosin based machinery of the malaria parasite.

7. A composition for inhibiting or preventing invasion of red blood cells by a malaria parasite comprising an agent, which inhibits interaction of the isolated protein of claim **1** with a host red blood cell or linkage of the isolated protein of claim **1** to a component of actin-myosin based machinery of the malaria parasite and a pharmaceutically acceptable carrier.

8. A method of preventing or decreasing clinical symptoms of malaria in a host infected with malaria comprising administering to the host the composition of claim **7**.

9. A vaccine comprising an antigen capable of invoking an immune response against the isolated protein of claim **1**.

10. A method for preventing malaria infection in a host at risk for malaria infection comprising administering to the host the vaccine of claim **9**.

11. An antibody which specifically binds the protein of claim **1** or a fragment thereof.

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专利名称(译)	用于预防和治疗疟疾感染的方法和组合物		
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摘要(译)

提供了分离的蛋白质和编码这种蛋白质的核酸序列，所述蛋白质与红细胞相互作用以被疟疾寄生虫侵入并与疟疾寄生虫的基于肌动蛋白 - 肌球蛋白的机器的组分连接。此外，还提供了鉴定抑制这些蛋白质作为治疗和预防疟疾感染的化学治疗剂和/或免疫剂的功能的药剂的方法。还提供了用于治疗和预防疟疾感染的组合物以及用于预防和治疗疟疾感染的方法。