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(54) Title: IDENTIFICATION GENES AND GENE PRODUCTS INVOLVED IN CYTOADHERANCE OF *PLASMODIUM* INFECTED ERYTHROCYTES

(57) **Abstract**

Cytoadherance Linked Asexual Genes (GLAGs) which facilitate cytoadherance of erythrocytes parasitised with *Plasmodium* species to other cells are identified.

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IDENTIFICATION GENES AND GENE PRODUCTS INVOLVED IN CYTOADHERANCE OF *PLASMODIUM* INFECTED ERYTHROCYTES

The present invention relates generally to a nucleic acid molecule from *Plasmodium* species which encodes a product involved in, associated with or which otherwise facilitates cytoadherence of cells parasitised with said *Plasmodium* species to other cells. The identification of this nucleic acid molecule permits the rational design of and screening for molecules capable of inhibiting or otherwise antagonising interaction between the translation product of the nucleic acid molecule on cells parasitised with the *Plasmodium* species and a receptor on cells which cytoadhere to said parasitised cells. The present invention extends to a family of nucleic acid molecules encoding cytoadherence molecules wherein the family comprises paralogues either binding to different ligands or at different stages of a parasite's life cycle. The present invention further provides a therapeutic agent useful for the prophylaxis and/or treatment of disease conditions caused or exacerbated by infection with *Plasmodium* species.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

The subject specification contains nucleotide and amino acid sequence information prepared using the programme PatentIn Version 2.0, presented herein after the bibliography. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, etc). The length, type of sequence (DNA, protein (PRT), etc) and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are defined by the information provided in numeric indicator field <400> followed by the sequence identifier (eg. <400>1, <400>2, etc).

The designation of nucleotide residues referred to herein are those recommended by the IUPAC-IUB Biochemical Nomenclature Commission, wherein A represents Adenine, C

represents Cytosine, G represents Guanine, T represents thymine, Y represents a pyrimidine residue, R represents a purine residue, M represents Adenine or Cytosine, K represents Guanine or Thymine, S represents Guanine or Cytosine, W represents Adenine or Thymine, H represents a nucleotide other than Guanine, B represents a nucleotide other than Adenine, V represents a nucleotide other than Thymine, D represents a nucleotide other than Cytosine and N represents any nucleotide residue.

Bibliographic details of the publications numerically referred to in this specification are collected at the end of the description.

The rapidly increasing sophistication of recombinant DNA technology is greatly facilitating research and development in the medical and allied health fields. This is particularly the case with respect to vaccine development for parasitic infection although the recombinant approach has not been applicable to all parasites. Species of the genus *Plasmodium* represent one important class of parasite for which hithertofore a recombinant approach to the development of therapeutic and prophylactic agents has proved somewhat elusive.

Malaria is a major disease caused by *Plasmodium* species. Of the human malaria parasites, *Plasmodium falciparum* is the most significant, being the major cause of morbidity and mortality in malaria-endemic areas. In addition, resistance to anti-malarial drugs is now widespread which is restricting the scope of therapeutic agents available to combat this debilitating disease. There is a need, therefore, for alternative therapeutic strategies in the prophylaxis and treatment of infection by *Plasmodium* species.

Severe malaria is associated with cytoadherence of infected red blood cells to the endothelial lining of capillaries and vesicles of various tissues including the brain. Ligands on the surface of parasitised red blood cells can bind to a number of endothelial cell receptors including CD36, ICAM1, thombospondin, chrondroitin-4-sulphate, VCAM-1, E selectin and PECAM-1 (1,2). A thorough understanding of the mechanisms behind cytoadherence is required before therapeutic agents blocking cytoadherence can be rationally designed.

The importance of electron-dense structures ("knobs") on the surface of the parasitised red blood cells to cytoadherence has long been recognised. A major constituent of knobs is the knob-associated histidine rich protein [KAHRP] (3), localised under the red cell membrane. During *in vitro* culture, some lines of *P. falciparum* lose the ability to produce knobs (4) and these organisms generally lose the ability to induce cytoadherence in parasitised host cells. This is a consequence of subtelomeric deletions in the region of chromosome 2 bearing the KAHRP gene (5). However, KAHRP is not the only molecule associated with cytoadherence since a clone has been reported to being able to adhere to melanoma cells although it is KAHRP$^-$ and knob$^-$ (6). Despite this, a targeted recombinational knockout of the KAHRP gene has been used to demonstrate that KAHRP itself is essential for knobs and for stable cytoadherence under physiological shear-stress levels (7).

Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) is a variable molecule of approximately 250 KDa located on the surface of the parasitised red blood cell (8). PfEMP1 is now used as a collective term for any product of the multigene *var* family and it is clear that the parasite can undergo clonal antigenic variation by switching on the expression of different members of this set of about 50 polymorphic genes (9-11). As switching can occur at up to 2% per generation, clonal parasite populations can express a mixture of PfEMP1 types even though only one or at most a few are expressed per cell. The PfEMP1 type expressed has an important role in determining the receptor specificity of the parasitised red blood cell (12).

However, these well-established components of cytoadherence represent only part of the picture. For example, the results of protease sensitivity studies have been explained by postulating a protease-insensitive common ligand in addition to the protease-sensitive variable PfEMP1 (12). Furthermore, there is considerable evidence that modification of the erythrocyte protein band 3 plays a role. Another candidate molecule with properties of a ligand has been termed "Sequestrin" (13). Currently, therefore, no coherent model can accommodate all these observations.

In accordance with the present invention, the inventors have now identified and cloned a genetic sequence from *Plasmodium* encoding a product required for cytoadherence. The genetic

sequence represents a member of a family of cytoadherence linked asexual genes *(clags)*. The identification of *clag* genetic species and the products encoded by these sequences enables a range of therapeutic agents to be rationally designed and/or identified and which are useful for the prophylaxis and treatment of disease conditions caused or exacerbated by infection by *Plasmodium* species.

A generalized gene encoding a cytoadherence linked asexual molecule is referred to herein as *"clag"*. The translation product is "CLAG". A particular paralogue is identified by the chromosome for which it is resident and number if there is more than one gene. For example, the *clag* gene described in Australian Patent Application No. PP2580 filed 25 March, 1998 is *"clag9"*. The two *clag* genes on chromosome 3 are referred herein as *clag3.1* and *clag3.2*. The *clag* gene on chromosome 2 is referred to herein as *"clag2"*.

In accordance with the present invention, a genetic sequence has been identified which encodes a protein which is involved in, associated with or which otherwise facilitates cytoadherence of red blood cells parasitised with a *Plasmodium* species to other cells.

Accordingly, one aspect of the present invention provides a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein involved in, associated with or which otherwise facilitates host cells parasitised with a *Plasmodium* species cytoadhering to other cells.

The cells parasitised by *Plasmodium* species are red blood cells. Generally, the nucleic acid molecules are in an isolated or purified form.

The present invention is particularly directed to and is exemplified by *Plasmodium falciparum*, the causative agent of malaria as the parasitising *Plasmodium* species. This is done, however, on the understanding that the subject invention extends to any species of *Plasmodium* which induce parasitised host cells to cytoadhere. Examples of *Plasmodium* species contemplated by the present invention include but are not limited to *Plasmodium malariae, Plasmodium ovale, Plasmodium cynomolgi, Plasmodium knowlesi, Plasmodium berghei* and *Plasmodium yoelii*.

Conveniently, the genetic sequence encoding the cytoadherence protein is referred to herein as a cytoadherence "gene". The term "gene" is used in its broadest context to refer to a genomic nucleotide sequence having introns and exons and which exons encoded a functional cytoadherence protein. The term "gene" also refers to a cDNA corresponding to the coding regions of the genomic gene and which encodes a functional cytoadherence protein. The cytoadherence gene of the present invention represents a family of cytoadherence genes located on different chromosomes. Each gene is a paralogue of each other. A paralogue is a gene or gene product generally involved in cytoadherence but which functions either at different levels of receptors or ligands or at different stages of the life cycle.

The cytoadherence gene of the present invention is one which encodes a product which:

(i) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to C32 melanoma cells;

(ii) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to endothelial cells;

(iii) is capable of binding or otherwise interacting with purified CD36;

(iv) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to endothelial cells at a particular life cycle stage; and/or

(v) is capable of interacting with the PfEMP1-KAHRD complex.

The product of the cytoadherence gene is not PfEMP1.

One *clag* gene is located within an approximately 55 kbp region of chromosome 9 of *P. falciparum* distal to the break point which commonly occurs in culture *in vitro* or a homologue of this region on another chromosome of *P. falciparum* or on a chromosome in another species of *Plasmodium* or a derivative of this region. This is referred to as *clag9*. Two other genes are located on chromosome 3 and are referred to as *clag3.1* and *clag3.2*. A gene on chromosome 2 is referred to as *clag2*.

Preferably, *clag9* is located within an approximately 7 kbp region of the 55 kbp portion of the

right hand end of chromosome 9 of *P. falciparum* or a homologue or derivative thereof. Even more preferably, the approximately 7 kbp region comprises at least about 3, still more preferably at least about 4, even more preferably at least about 5 exons, and still more preferably at least about 6-9 exons such as 9 exons.

Accordingly, another aspect of the present invention is directed to a sequence of nucleotides encoding or complementary to a sequence encoding a protein involved in, associated with or which otherwise facilitates red blood cells parasitised with *Plasmodium* species cytoadhering to C32 melanoma cells or endothelial cells or purified CD36 wherein said nucleic acid molecule corresponds to a nucleotide sequence located within the 55 kbp region at the right hand end of chromosome 9 and comprises at least about 5 exons within a region of 7 kbp located just distal to a common break point of *P. falciparum* or a homologue or derivative of said region or a paralogue of this nucleic acid molecule.

The "break point" refers to the point on the chromosome in which cleavage commonly occurs such as when the parasite is cultured.

The cytoadherence gene of the present invention comprises, in a particularly preferred embodiment, a nucleotide sequence which encodes an amino acid sequence substantially as set forth in <400>2 (CLAG9) or <400>11 (CLAG3.1) or <400>12 (CLAG3.2) or <400>13 (CLAG2) or an amino acid sequence having at least 35% similarity to at least about 20 contiguous amino acids of <400>2 or <400>11 or <400>12 or <400>13. Preferably, the 35% similarity is determined with respect to the entire amino acid sequence of <400>2 or <400>11 or <400>12 or <400>13.

The term "similarity" as used herein includes exact identity between compared sequences at the nucleotide or amino acid level. Where there is non-identity at the nucleotide level, "similarity" includes differences between sequences which result in different amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. Where there is non-identity at the amino acid level, "similarity" includes amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational

levels. In a particularly preferred embodiment, nucleotide and sequence comparisons are made at the level of identity rather than similarity. Any number of programs are available to compare nucleotide and amino acid sequences. Preferred programs have regard to an appropriate alignment. One such program is Gap which considers all possible alignment and gap positions and creates an alignment with the largest number of matched bases and the fewest gaps. Gap uses the alignment method of Needleman and Wunsch (*J. Mol. Biol. 48:* 443-453, 1970). Gap reads a scoring matrix that contains values for every possible GCG symbol match. GAP is available on ANGIS (Australian National Genomic Information Service) at website http://mel1.angis.org.au.

Alternative percentage similarities to <400>2 or <400>11 or <400>12 or <400>13 encompassed by the present invention include at least about 40% at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or above.

The amino acid sequence represented by <400>2 corresponds to a protein referred to herein as "CLAG9" and is the product of *clag9*. <400>11 and <400>12 correspond to CLAG3.1 and CLAG3.2, respectively which are encoded by *clag3.1* and *clag*3.2. <400>13 corresponds to CLAG2 encoded by *clag2*. Reference herein to "CLAG9" or "CLAG3.1" or "CLAG3.2" or "CLAG2" includes reference to the protein defined by the amino acid sequence of <400>2 or <400>11 or <400>12 or <400>13, respectively or a derivative or homologue thereof having at least 35% similarity to the amino acid sequence of <400>2 or <400>11 or <400>12 or <400>13. A "derivative" includes a fragment, portion or part of CLAG as well as any single or multiple amino acid substitutions, additions and/or deletions to the amino acid sequence set forth in <400>2 or <400>11 or <400>12 or <400>13. As stated above, CLAG is preferably from *P. falciparum* although the present invention extends to any homologue or paralogue having at least 35% similarity to <400>2 encoded by a gene on another chromosome of *P. falciparum* or by a gene in the genome of another species of *Plasmodium*. An example of a paralogue is a similar genetic sequence on chromosome 3 of *P. falciparum* which encodes an amino acid sequence having approximately 60% similarity to <400>5 or <400>11 or <400>12.

According to these embodiments, there is provided a sequence of nucleotides encoding or complementary to a sequence encoding a protein involved in, associated with or which otherwise facilitates red blood cells parasitised with *Plasmodium* species cytoadhering to C32 melanoma cells or endothelial cells or to purified CD36 wherein said nucleotide sequence encodes an amino acid sequence substantially as set forth in <400>2 or <400>11 or <400>12 or <400>13 or an amino acid sequence having at least 35% similarity to at least about 20 contiguous amino acids of <400>2 or <400>11 or <400>12 or <400>13.

In a particularly preferred embodiment, CLAG9 is encoded by a nucleotide sequence substantially as set forth in <400>1 or a nucleotide sequence having at least about 35% similarity to at least about 60 contiguous nucleotides of <400>1. Preferably, however, the 35% similarity is over the entire nucleotide sequence of <400>1. Alternative percentage similarities to the nucleotide sequence of <400>1 include at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or above.

The nucleotide sequence of <400>1 is referred to as the clag9 gene and encodes CLAG9. Reference herein to a *clag* gene includes all derivatives, homologues and paralogues thereof. A homologue or a paralogues of *clag* includes a nucleotide sequence on a different chromosome of *P. falciparum* or on a chromosome of another species of *Plasmodium.*

A "derivative" of *clag9* includes fragments, portions and parts of the nucleotide sequence set forth in <400>1 as well as single or multiple nucleotide substitutions, additions and/or deletions to the nucleotide sequence of <400>1.

A derivative and homologue is also conveniently defined as any nucleotide sequence capable of hybridizing to <400>1 under low stringency conditions.

Reference herein to a low stringency includes and encompasses from at least about 0% v/v to at least about 15% v/v formamide and from at least about 1M to at least about 2M salt for

hybridisation, and at least about 1M to at least about 2M salt for washing conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5M to at least about 0.9M salt for hybridisation, and at least about 0.5M to at least about 0.9M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least about 0.01M to at least about 0.15M salt for hybridisation, and at least about 0.01M to at least about 0.15M salt for washing conditions. Generally, low stringency conditions are determined at from about 25 to about 48°C such as 42°C medium stringency in from about 40 to 55°C. High stringency in general from about 50 to about 65°C.

Accordingly, another aspect of the present invention is directed to a sequence of nucleotides encoding or complementary to a sequence encoding a protein involved in, associated with or which otherwise facilitates red blood cells parasitised with *Plasmodium* species cytoadhering to C32 melanoma cells endothelial cells and/or purified CD36 wherein said nucleotide sequence is as set forth in <400>1 or a nucleotide sequence having at least 35% similarity to 60 contiguous nucleotides of <400>1.

Another aspect of the present invention provides an isolated nucleic acid molecule having one or more of the following characteristics:

(i) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to C32 melanoma cells;

(ii) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to endothelial cells;

(iii) encodes a product capable of binding or otherwise interacting with CD36;

(iv) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to endothelial cells at a particular life cycle stage;

(v) encodes a product capable of interacting with PfEMP1-KAHRP complex but is not PfEMP1;

(vi) comprises a nucleotide sequence substantially as set forth in <400>1 or a nucleotide sequence having at least 35% similarity to <400>1 and/or is capable of hybridising to <400>1

under low stringency conditions; and/or

(vii) encodes a product comprising an amount and sequence substantially as set forth in <400>2 or <400>11 or <400>12 or <400>13 or an amino acid sequence having at least 30% similarity thereto.

In a particularly preferred embodiment, the present invention provides an isolated nucleic acid molecule having the following characteristics:

(i) is derived from the region of about 55 kbp of the right hand end of chromosome 9 of *P. falciparum* or an equivalent region on another chromosome of *P. falciparum* or a chromosome of another *Plasmodium* species;

(ii) encodes a protein enabling cells expressing said protein to adhere to melanoma cells;

(iii) encodes a protein having an amino acid sequence substantially as set forth in <400>2 or an amino acid sequence having at least 35% similarity to <400>2; and

(iv) comprises a nucleotide sequence which:

(a) is as substantially set forth in <400>1; or

(b) has at least 35% similarity to <400>1; and/or

(c) is capable of hybridizing to <400>1 under low stringency conditions at 42°C.

The present invention further extends to antisense molecules to the *clag* genetic sequence as well as ribozyme and deoxyribozyme molecules and molecules suitable for use as co-suppression agents.

Accordingly, another aspect of the present invention comprises an oligonucleotide comprising at least about 10 nucleotides, preferably at least about 13-18 nucleotides and more preferably at least about 20 nucleotides capable of hybridizing under low stringency conditions to mRNA transcribed from *clag* DNA.

More particularly, this aspect of the present invention contemplates an antisense molecule comprising at least about 10 nucleotides, preferably , preferably at least about 13-18 nucleotides and more preferably at least about 20 nucleotides capable of hybridizing or otherwise forming

a duplex with mRNA corresponding to all or part of the nucleotide sequence set forth in <400>1 or to a nucleotide sequence having at least 35% similarity thereto or a sequence capable of hybridizing to <400>1 under low stringency conditions and wherein said antisense molecule is capable of reducing the amount of protein translated from said mRNA.

The reduction in CLAG protein in accordance with the above embodiment of the present invention means a reduction in at least about 10%, more preferably at least about 20%, still more preferably at least about 30%, even still more preferably at least about 40% and yet even more preferably greater than 50% compared to expression of *clag* in the absence of the antisense molecule.

The antisense molecule is conveniently at least 10 nucleotides in length but is more preferably at least about 13 nucleotides or greater such as at least about 20 nucleotides, 30 nucleotides or 40 nucleotides. Alternatively, the entire *clag* gene is used in its reverse orientation or a derivative, part, portion or fragment of the *clag* gene in reverse orientation.

Ribozymes may be constructed by any convenient means such as by referring to in International Patent Application Publication No. WO 98/05852 or the disclosure of Haselhoff and Gerlach (18). Ribozymes are constructed with a hybridizing region which is complimentary to at least part of a target RNA which, in this case, encodes CLAG. The activity of ribozymes is measurable, for example, on Northern blots.

According to this embodiment, there is provided a ribozyme comprising a hybridizing region and a catalytic region wherein the hybridizing region is capable of hybridizing to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to <400>1 or a gene having at least 35% similarity to a cDNA molecule corresponding to <400>1 or a nucleotide sequence capable of hybridizing under low stringency conditions to <400>1 and wherein said catalytic domain is capable of cleaving said target mRNA to reduce or inhibit translation of the mRNA molecule.

The present invention further extends to molecules capable of co-suppression of an endogenous

clag gene or its derivatives or homologues. Generally, the entire *clag* sequence or its derivative or homologue is used or a 3′ end portion, a 5′ end portion or an internal fragment may also be used.

The present invention further extends to a range of genetic constructs comprising the *clag* gene or derivatives or homologues thereof. Generally, the genetic construct comprises a *clag* gene sequence or a derivative or homologue thereof operably linked to a promoter. The *clag* gene sequence may also be fused to another genetic sequence such as a reporter gene sequence or a sequence encoding an amino acid sequence to facilitate purification of CLAG such as a nucleotide sequence encoding FLAG.

Yet another aspect of the present invention contemplates a purified CLAG protein.

According to this aspect of the present invention, there is provided an isolated protein involved in, associated with or which otherwise facilitates host cells parasitised with *Plasmodium* species cytoadhering to other cells.

More particularly, the present invention is directed to an isolated protein involved in, associated with or which otherwise facilitates red blood cells parasitised with *Plasmodium* species cytoadhering to melanoma cells.

In a preferred embodiment, the present invention contemplates an isolated protein involved in, associated with or which otherwise facilitates red blood cells parasitised with *Plasmodium* species cytoadhering to C32 melanoma cells or endothelial cells or purified CD36.

A further preferred embodiment provides an isolated protein having one or more of the following characteristics:

(i) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to C32 melanoma cells;

(ii) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to endothelial cells;

(iii) encodes a product capable of binding or otherwise interacting with CD36;

(iv) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to endothelial cells at a particular life cycle stage;

(v) encodes a product capable of interacting with a PfEMP1-KAHRP complex but is not PfEMP1;

(vi) comprises a nucleotide sequence substantially as set forth in <400>1 or a nucleotide sequence having at least 35% similarity to <400>1 and/or is capable of hybridising to <400>1 under low stringency conditions; and/or

(vii) encodes a product comprising an amount and sequence substantially as set forth in <400>2 or <400>11 or <400>12 or <400>13 or an amino acid sequence having at least 30% similarity thereto.

In a particularly preferred embodiment, the present invention is directed to an isolated protein involved in, associated with or which otherwise facilitates red blood cells parasitised with *Plasmodium* species cytoadhering to C32 melanoma cells or endothelial cells or purified CD36 wherein said protein comprises an amino acid sequence substantially as set forth in <400>2 or <400>11 or <400>12 or <400>13 or an amino acid sequence having at least 35% similarity to at least about 20 contiguous amino acids of <400>2 or <400>11 or <400>12 or <400>13.

The protein of this aspect of the present invention is referred to as CLAG. Preferably, CLAG is in recombinant form. Reference herein to "CLAG" includes all derivatives, homologues and mimetics thereof as well as recombinant, synthetic or isolated naturally occurring forms of CLAG. A derivative as stated above includes mutants, fragments, parts and portions thereof such as single or multiple amino acid substitutions, additions and/or deletions of CLAG. A derivative of CLAG also encompasses chemical analogues of CLAG and peptides and peptide mimetics of certain regions of CLAG such as regions comprising B-cell and T-cell epitopes, a transmembrane domain, an extracellular domain and/or a cytoplasmic domain. The use of chemical analogues may be useful in stabilizing the CLAG molecule for use as a diagnostic agent or in screening for agents capable of interacting with CLAG such as in immunoassays or natural product screening.

Analogues of CLAG contemplated herein include, but are not limited to, modification to side chains, incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogues.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with $NaBH_4$.

The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivitisation, for example, to a corresponding amide.

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acid, contemplated herein is shown in Table 1.

TABLE 1

Non-conventional amino acid	Code	Non-conventional amino acid	Code
α-aminobutyric acid	Abu	L-N-methylalanine	Nmala
α-amino-α-methylbutyrate	Mgabu	L-N-methylarginine	Nmarg
aminocyclopropane-carboxylate	Cpro	L-N-methylasparagine	Nmasn
		L-N-methylaspartic acid	Nmasp
aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbornyl-carboxylate	Norb	L-N-methylglutamine	Nmgln
		L-N-methylglutamic acid	Nmglu
cyclohexylalanine		Chexa L-N-methylhistidine	Nmhis
cyclopentylalanine	Cpen	L-N-methylisolleucine	Nmile
D-alanine	Dal	L-N-methylleucine	Nmleu
D-arginine	Darg	L-N-methyllysine	Nmlys
D-aspartic acid	Dasp	L-N-methylmethionine	Nmmet
D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
D-isoleucine	Dile	L-N-methylproline	Nmpro
D-leucine	Dleu	L-N-methylserine	Nmser
D-lysine	Dlys	L-N-methylthreonine	Nmthr
D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
D-phenylalanine	Dphe	L-N-methylvaline	Nmval
D-proline	Dpro	L-N-methylethylglycine	Nmetg
D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
D-threonine	Dthr	L-norleucine	Nle
D-tryptophan	Dtrp	L-norvaline	Nva

D-tyrosine	Dtyr	α-methyl-aminoisobutyrate	Maib
D-valine	Dval	α-methyl-γ-aminobutyrate	Mgabu
D-α-methylalanine	Dmala	α-methylcyclohexylalanine	Mchexa
D-α-methylarginine	Dmarg	α-methylcylcopentylalanine	Mcpen
D-α-methylasparagine	Dmasn	α-methyl-α-napthylalanine	Manap
D-α-methylaspartate	Dmasp	α-methylpenicillamine	Mpen
D-α-methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
D-α-methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
D-α-methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
D-α-methylisoleucine	Dmile	N-amino-α-methylbutyrate	Nmaabu
D-α-methylleucine	Dmleu	α-napthylalanine	Anap
D-α-methyllysine	Dmlys	N-benzylglycine	Nphe
D-α-methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
D-α-methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
D-α-methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
D-α-methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
D-α-methylserine	Dmser	N-cyclobutylglycine	Ncbut
D-α-methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
D-α-methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
D-α-methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
D-α-methylvaline	Dmval	N-cylcododecylglycine	Ncdod
D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
D-N-methylhistidine	Dnmhis	N-(hydroxyethyl))glycine	Nser
D-N-methylisoleucine	Dnmile	N-(imidazolylethyl))glycine	Nhis
D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp

D-N-methyllysine	Dnmlys	N-methyl-γ-aminobutyrate	Nmgabu
N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen
N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
D-N-methyltyrosine	Dnmtyr	N-methyla-napthylalanine	Nmanap
D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
γ-aminobutyric acid	Gabu	N-(*p*-hydroxyphenyl)glycine	Nhtyr
L-*t*-butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
L-ethylglycine	Etg	penicillamine	Pen
L-homophenylalanine	Hphe	L-α-methylalanine	Mala
L-α-methylarginine	Marg	L-α-methylasparagine	Masn
L-α-methylaspartate	Masp	L-α-methyl-*t*-butylglycine	Mtbug
L-α-methylcysteine	Mcys	L-methylethylglycine	Metg
L-α-methylglutamine	Mgln	L-α-methylglutamate	Mglu
L-α-methylhistidine	Mhis	L-α-methylhomophenylalanine	Mhphe
L-α-methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
L-α-methylleucine	Mleu	L-α-methyllysine	Mlys
L-α-methylmethionine	Mmet	L-α-methylnorleucine	Mnle
L-α-methylnorvaline	Mnva	L-α-methylornithine	Morn
L-α-methylphenylalanine	Mphe	L-α-methylproline	Mpro
L-α-methylserine	Mser	L-α-methylthreonine	Mthr
L-α-methyltryptophan	Mtrp	L-α-methyltyrosine	Mtyr

L-α-methylvaline	Mval	L-N-methylhomophenylalanine	Nmhphe
N-(N-(2,2-diphenylethyl) carbamylmethyl)glycine	Nnbhm	N-(N-(3,3-diphenylpropyl) carbamylmethyl)glycine	Nnbhe
1-carboxy-1-(2,2-diphenyl-ethylamino)cyclopropane	Nmbc		

These types of modifications may be important to stabilise CLAG if administered to an individual or for use as a diagnostic reagent.

Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety.

In addition, peptides can be conformationally constrained by, for example, incorporation of C_α and N_α-methylamino acids, introduction of double bonds between C_α and C_β atoms of amino acids and the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two side chains or between a side chain and the N or C terminus.

The present invention further contemplates chemical analogues of CLAG capable of acting as antagonists of CLAG or which can act as functional analogues of CLAG. Chemical analogues may not necessarily be derived from CLAG but may share certain conformational similarities. Alternatively, chemical analogues may be specifically designed to mimic certain physiochemical properties of CLAG. Chemical analogues may be chemically synthesised or may be detected following, for example, natural product screening of environments such as the ocean, coral, seabeds, rivers, riverbeds, antarctic regions, plants, bacteria and eukaryotic organisms.

The identification of CLAG permits the generation of a range of molecules capable of

modulating expression of *clag* or modulating the activity of CLAG. Modulators contemplated by the present invention include antagonists of *clag* expression. Antagonists of *clag* expression include antisense molecules, ribozymes and co-suppression molecules. Antagonists of CLAG activity include antibodies and inhibitor peptide fragments.

Another embodiment of the present invention contemplates a method for modulating expression of *clag* in a mammal, said method comprising contacting the *clag* gene encoding CLAG with an effective amount of a modulator of *clag* expression for a time and under conditions sufficient to down-regulate or otherwise modulate expression of *clag*. For example, an anti-sense nucleic acid molecule to *clag* or a derivative thereof may be introduced into a cell to reduce the *clag* expression to reduce cytoadherence of that cell to another cell.

Another aspect of the present invention contemplates a method of modulating activity of CLAG in a mammal, said method comprising administering a modulating effective amount of a molecule for a time and under conditions sufficient to decrease CLAG activity. The molecule may be a proteinaceous molecule or a chemical entity and may also be a derivative of CLAG or its receptor or a chemical analogue or truncation mutant of CLAG or its receptor.

The preferred mammal is a human.

The present invention further contemplates a composition comprising CLAG or a derivative thereof or a modulator of CLAG expression or *clag* activity and one or more pharmaceutically acceptable carriers and/or diluents. These components are referred to as the "active ingredients".

Composition forms suitable for injectable use include sterile aqueous solutions (where water soluble) and sterile powders for the extemporaneous preparation of sterile injectable solutions. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

The carrier can be a solvent or dispersion medium containing, for example, water, ethanol,

polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimersal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active ingredients in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by an appropriate form of sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 μg and 2000 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter: a binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such a sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active ingredients may be incorporated into sustained-release preparations and formulations. The active ingredients may also be administered sequentially or simultaneously with other active compounds such as anti-malaria drugs, anti-biotics or fever reducing compounds. The term "sequentially" includes the administration of two or more compounds within seconds, minutes, hours, days or weeks.

Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly

dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from 0.5 μg to about 2000 mg. Expressed in proportions, the active compound is generally present in from about 0.5 μg to about 2000 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients. Alternatively, active ingredients may be administered in amounts ranging from about 0.1 μg/kg body weight to about 10 mg/kg body weight. They may be administered per hour, day, two days, week or months.

The formulation of compositions is generally known in the art and reference can conveniently be made to Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Co., Easton, Pennsylvania, USA.

A particularly useful form of the composition is a recombinant active ingredient produced, for example, in a vaccine vector, such as but not limited to a vaccinia virus vector or bacterial cell capable of expressing the active ingredient. The active ingredient may be produced with a patient or in cell culture and then administered to a patient.

The present invention clearly extends to recombinant compositions in which the active ingredient at least is contained within killed vaccine vectors prepared, for example, by heat, formalin or other chemical treatment, electric shock or high or low pressure forces. According to this embodiment, the active ingredient of the composition is generally synthesized in a live vaccine vector which is killed prior to administration to an animal.

Furthermore, the vaccine vector expressing the active ingredient may be non-pathogenic or attenuated. Within the scope of this embodiment are non-pathogenic or attenuated viruses and bacteria which express the active ingredient of the composition and non-pathogenic or attenuated viruses which express the active ingredient and are contained within a non-pathogenic or attenuated host cell.

Attenuated or non-pathogenic host cells include those cells which are not harmful to an animal to which the subject composition is administered. As will be known to those skilled in the art, "live vaccines" can comprise an attenuated virus vector expressing the active ingredient or a host cell comprising same, which is capable of replicating in an animal to which it is administered, albeit producing no adverse side-effects therein. Such vaccine vectors may colonise the gut or other organ of the vaccinated patient. Such live vaccine vectors are efficacious by virtue of their ability to continually express the active ingredient in the host animal for a time and at a level sufficient to confer protective immunity against a pathogen which expresses an immunogenic or functional equivalent of said active ingredient. The present invention clearly encompasses the use of such attenuated or non-pathogenic vectors and live vaccine preparations.

The vaccine vector may be a virus, bacterial cell or a eukaryotic cell such as an avian, porcine or other mammalian cell or a yeast cell or a cell line such as COS, VERO, HeLa, mouse C127, Chinese hamster ovary (CHO), WI-38, baby hamster kidney (BHK) or MDCK cell lines. Suitable prokaryotic cells include *Mycobacterium spp., Corynebacterium spp., Salmonella spp., Escherichia coli, Bacillus spp.* and *Pseudomonas spp*, amongst others. Bacterial strains which are suitable for the present purpose are well-known in the relevant art.

Such cells and cell lines are capable of expression of a genetic sequence encoding a peptide, polypeptide or protein of the present invention which antagonises CLAG function in a manner effective to induce a protective response in the patient. For example, a non-pathogenic bacterium could be prepared containing a recombinant sequence capable of encoding a CLAG antagonist. The recombinant sequence would be in the form of an expression vector under the control of a constitutive or inducible promoter. The bacterium would then be permitted to

colonise suitable locations in a patient's gut and would be permitted to grow and produce the recombinant molecule in amount sufficient to induce a protective response against *Plasmodium.*

In a further alternative embodiment, the composition may comprise a DNA vaccine comprising a DNA molecule encoding a peptide, polypeptide or protein of the present invention and which is injected into muscular tissue or other suitable tissue in a patient under conditions sufficient to permit transient expression of said DNA to produce an amount of peptide, polypeptide or protein effective to induce a protective response.

Still another aspect of the present invention is directed to antibodies to CLAG and its derivatives. Such antibodies may be monoclonal or polyclonal and may be selected from naturally occurring antibodies to CLAG or may be specifically raised to CLAG or derivatives thereof. In the case of the latter, CLAG or its derivatives may first need to be associated with a carrier molecule. Particularly useful derivatives are peptide fragments of CLAG proteins such as but not limited to peptides defined in <400>14, <400>15 and <400>16 or homologues or derivatives thereof. The antibodies and/or recombinant CLAG or its derivatives (including peptide fragments) of the present invention are particularly useful as therapeutic, diagnostic and/or selection agents.

For example, CLAG and its derivatives can be used to screen for naturally occurring antibodies to CLAG. Alternatively, specific antibodies can be used to screen for CLAG. Techniques for such assays are well known in the art and include, for example, sandwich assays and ELISA. Knowledge of CLAG levels may be important for diagnosis of certain disease conditions such as malaria or a predisposition to disease conditions such as malaria or for monitoring certain therapeutic protocols.

Antibodies to CLAG of the present invention may be monoclonal or polyclonal. Alternatively, fragments of antibodies may be used such as Fab fragments. Furthermore, the present invention extends to recombinant and synthetic antibodies and to antibody hybrids. A "synthetic antibody" is considered herein to include fragments and hybrids of antibodies. The antibodies of this aspect of the present invention are particularly useful for immunotherapy in the

prophylaxis and treatment of *Plasmodium* infection and may also be used as a diagnostic tool for assessing *Plasmodium* infection or monitoring the program of a therapeutic regimin.

For example, specific antibodies can be used to screen for CLAG proteins. The latter would be important, for example, as a means for screening for levels of CLAG in a cell extract or other biological fluid or purifying CLAG made by recombinant means from culture supernatant fluid. Techniques for the assays contemplated herein are known in the art and include, for example, sandwich assays and ELISA.

It is within the scope of this invention to include any second antibodies (monoclonal, polyclonal or fragments of antibodies or synthetic antibodies) directed to the first mentioned antibodies discussed above. Both the first and second antibodies may be used in detection assays or a first antibody may be used with a commercially available anti-immunoglobulin antibody. An antibody as contemplated herein includes any antibody specific to any region of CLAG.

Both polyclonal and monoclonal antibodies are obtainable by immunization with the enzyme or protein and either type is utilizable for immunoassays. The methods of obtaining both types of sera are well known in the art. Polyclonal sera are less preferred but are relatively easily prepared by injection of a suitable laboratory animal with an effective amount of CLAG, or antigenic parts thereof, collecting serum from the animal, and isolating specific sera by any of the known immunoadsorbent techniques. Although antibodies produced by this method are utilizable in virtually any type of immunoassay, they are generally less favoured because of the potential heterogeneity of the product.

The use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for monoclonal antibody production derived by fusing an immortal cell line and lymphocytes sensitized against the immunogenic preparation can be done by techniques which are well known to those who are skilled in the art.

Another aspect of the present invention contemplates a method for detecting CLAG in a

biological sample from a mammal said method comprising contacting said biological sample with an antibody specific for CLAG or its derivatives or homologues for a time and under conditions sufficient for an antibody-CLAG complex to form, and then detecting said complex. The presence of said complex would then be indicative of the presence of CLAG.

The presence of CLAG may be accomplished in a number of ways such as by Western blotting and ELISA procedures. A wide range of immunoassay techniques are available as can be seen by reference to US Patent Nos. 4,016,043, 4, 424,279 and 4,018,653. These, of course, include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labelled antibody to a target.

Sandwich assays are among the most useful and commonly used assays and are favoured for use in the present invention. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabelled antibody specific for CLAG or a molecule fused to CLAG is immobilized on a solid substrate and the sample to be tested brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-CLAG complex, a second antibody specific to CLAG, labelled with a reporter molecule capable of producing a detectable signal, is then added and incubated, allowing time sufficient for the formation of another complex of antibody-CLAG-labelled antibody. Any unreacted material is washed away and the presence of the antigen is determined by observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of hapten. Variations on the forward assay include a simultaneous assay, in which both sample and labelled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including any minor variations as will be readily apparent. In addition, CLAG receptors may be employed to form a complex or cytoadherence or inhibitor of cytoadherence may be employed in the assay. In accordance with the present invention, the sample is one which might contain CLAG including cell extract, tissue biopsy or whole blood. The sample is, therefore, generally a biological sample comprising

biological fluid but also extends to fermentation fluid and supernatant fluid such as from a cell culture.

In the typical forward sandwich assay, a first antibody having specificity for the CLAG or antigenic parts thereof, is either covalently or passively bound to a solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a sufficient period of time (e.g. 2-40 minutes or overnight if more convenient) and under suitable conditions (e.g. from room temperature to 37°C) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the hapten. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to CLAG.

An alternative method involves immobilizing the target CLAG molecules in a biological sample and then exposing the immobilized target to specific antibody which may or may not be labelled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labelling with the antibody. Alternatively, a second labelled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

By "reporter molecule" as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-bound antibody. Detection may be either qualitative or quantitative. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores or radionuclide containing molecules (i.e. radioisotopes) and chemiluminescent molecules.

In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable colour change. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labelled antibody is added to the first antibody-CLAG complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-CLAG-antibody. The substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of hapten which was present in the sample. "Reporter molecule" also extends to use of cell cytoadherence or inhibition of cytoadherence such as red blood cells on latex beads and the like.

Alternately, fluorescent compounds, such as fluorescein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labelled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. As in the EIA, the fluorescent labelled antibody is allowed to bind to the first antibody-CLAG complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength the fluorescence observed indicates the presence of CLAG. Immunofluorescene and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

The nucleotide sequence corresponding to *clag9* has been deposited in GenBank under Serial No. 181394, 25 March, 1998. The nucleotide sequence of *clag3.1* and *clag3.2* is under Serial Number Z97348 and *clag2* is under Serial Number AE001428 of GenBank.

The present invention is further described by the following non-limiting Figures and Examples.

In the Figures:

Figure 1 is a diagrammatic representation of the relationship of the *clag* gene to deletions at the right end of chromosome 9. The right end of chromosome 9 from cytoadherent isolate 1776 (19), from non-cytoadherent clone C10 derived from 1776 (19), and from B8, a cytoadherent clone derived from ItG2 (6) are shown. The telomere of each chromosome is indicated (Tel). YAC 773 containing the cytoadherence locus has been described (14). Splicing of *clag* mRNA is indicated. The four shaded regions of the CLAG protein indicate the transmembrane regions predicted with the highest degree of certainty in Figure 3.

Figure 2 is a photographic representation showing expression of *clag9* in blood stages. mRNA prepared using a Pharmacia Quick Prep mRNA purification kit according to the manufacturers instructions was copied with reverse transcriptase using a Pharmacia Read to Go T-primed first strand kit. The resulting cDNA was amplified by PCR using oligonucleotide CAG TGT TTT TAA TAG TGA TC [<400>3] and AAG ATT TGC AGG TGT TTC G [<400>4]. Track 1, 3D7 DNA; Track 2, 3D7 cDNA.

Figure 3 is a graphical representation showing hydrophobicity of CLAG9. The *clag9* cDNA sequence was analysed using the program TopPred11.

Figure 4A is a diagrammatic representation showing the structure of antisense construct HC.ASC1, based on vector HC1 (16). Arrows show the positions of the PCR primers used. HSP86, 3′ Heat shock protein 86 3′ untranslated sequence. Cam 5′, Calmodulin 5′ untranslated region. Tg DHFR-TS, *Toxoplasma gondii* dihydrofolate reductase-thymidylate synthase. PcDT 5′, *Plasmodium chabaudi* DHFR-TS 5′ untranslated region. HRP2 3′, Histidine rich protein 2 3′′ untranslated region.

Figure 4B is a photographic representation of PCR reactions to test for the presence of episomal and integrated forms of HC.ASCI. M, 1/*Hind* III markers. Lanes 1-4, 3D7 DNA.

Lanes 5-8, 3D7.HC.ASC1 DNA at 9 weeks at culture. Lanes 9-12, 3D7.HC.ASC1 DNA at 15 weeks of culture. Lanes 1, 5, 9 divergent primers Cso 46 and Xho R (test for circular vector). Lanes 2, 6, 10, primers Xho F plus Xho R (test for vector insert). Lanes 3, 7, 11, primers 5X′ plus 3X′ *(clag* gene test). Lanes 4, 8, 12, primers S2E5 plus Xho R (integration test). A PCR product could only have been present in lanes 8 and 12 if HC.ASC1 had integrated into chromosome 9 of 3D7 as primer S2E5 lies 5′ to the region of *clag9* inserted into the HC1 vector.

Figure 5 is a photographic representation showing southern blotting experiments to test for the presence of episomal and integrated forms of HC.ASC1.

A. 3D7 (Lane 1) and 3D7.HC.ASC1 (Lane 2) genomic DNA digested with *Bg/*II (which linearises the HC.ASC1 plasmid, see Figure 4) was fractionated by agarose gel electrophoresis, blotted and probed for the clag insert present in the plasmid.

B. Genomic DNA digested with *Bg/*I was fractionated by pulsed field electrophoresis and probe for the 5′ region of *clag* that is not present in the plasmid. 3D7 (Lane 1) and 3D7.HC.AS (Lane 2) have an approximately 180 kb *Bg/*I fragment whereas a 3D7 clone with a vector integrated into the *clag* gene (Lane 3) has a 70 kb fragment as the integrated vector introduces an additional *Bg/*I site.

Figure 6A is a diagrammatic representation showing structure of the chromosomal copy of *clag9.* Arrows indicate primer locations.

Figure 6B is a diagrammatic representation showing structure of the knockout construct pAC4-CLAG. Large arrows indicate the plasmid backbone, small arrows indicate primer locations.

Figure 6C is a photographic representation showing PCR reactions testing for the presence of vector integrated into the chromosomal copy of *clag9.* Lanes 1-5 3D7 DNA, lanes 6-10 *clag* transfectant DNA 19 weeks post transfection. Lanes 1 and 6, primers for the KAHRP gene. Lanes 2 and 7, primers Csol and S2EB (test for uninterrupted *clag* 9). Lanes 3 and 8, primers Csol and DCH42 (integration test). Lanes 4 and 9, primers LAV2 and S2EB (integration test).

Lanes 5 and 10, negative control.

Figure 7 is a photographic representation of indirect immunofluorescence staining. The figure shows the staining pattern produced on acetone fixed film of *P. falciparum* trophozoites by antibodies to CLAG9 peptide 3 (<400>16).

Figure 8 is a photographic representation of the *clag* gene family. A probe derived from a relatively conserved region and generated by PCR with the corresponding primers was hybridised to chromosomes of 3D7 after separation by pulsed field electrophoresis.

Figure 9 is a representation of amino acid sequences for CLAG3.1 (<400>11), CLAG3.2 (<400>12), CLAG2 (<400>13) and CLAG9 (<400>2).

Figure 10 is a graphical representation of hydrophobicity profiles of three clag gene family members. Predicted hydrophobicity profiles **a)** clag2, **b)** clag3.1, and **c)** clag9 using the TropPred II algorithm.

Figure 11 is a photographic representation showing surface proteins of clone 3D7 and TGD clone 11E were iodinated with ^{125}I. The samples were then divided into two and half of each was subjected to mild trypsinisation. The samples were then extracted sequentially with Factor x100 followed by SDS. The SDS extracts were fractionated on an SDS-polyacrylamide gel and autoradiographed.

TABLE 2

SUMMARY OF SEQUENCES IN SEQUENCE LISTING

Numeric Indicator	Sequence
<400>1	Nucleotide sequence of *clag9*
<400>2	Amino acid sequence of CLAG9
<400>3	PCR oligonucleotide for *clag9*
<400>4	PCR oligonucleotide for *clag9*
<400>5	Nucleotide sequence of paralogue *clag9* on chromosome 3
<400>6	Amino acid sequence of paralogue of CLAG9 on chromosome 3
<400>7	Oligonucleotide sequence
<400>8	Oligonucleotide sequence
<400>9	Oligonucleotide sequence
<400>10	Oligonucleotide sequence
<400>11	Amino acid sequence of CLAG3.1
<400>12	Amino acid sequence of CLAG3.2
<400>13	Amino acid sequence of CLAG2
<400>14	Peptide fragment of CLAG9
<400>15	Peptide fragment of CLAG9
<400>16	Peptide fragment of CLAG9

EXAMPLE 1

The Cytoadherence Locus on Chromosome 9

The inventors have identified a gene product which is essential for cytoadherence. During *in vitro* cultivation, isolates of *P. falciparum* commonly undergo loss of cytoadherence, as measured by binding to C32 melanoma cells (4). The inventors have associated this loss with subtelomeric deletions of chromosome 9 [19-21] (Figure 1). Independent deletion breakpoints in a number of independent strains were tightly clustered (14). Binding a mixed parasite population (containing deleted and non-deleted forms derived from the same parental line) to melanoma cells resulted in selection of parasites with the undeleted form of chromosome 9 in all 4 lines tested. The inventors proposed that a gene essential for cytoadherence is located in this region.

The product of such a gene may associate with the PfEMP1-KAHRP complex or may be independently expressed at the surface of the red cell. Alternatively it may be necessary for transport, processing or regulation of *var* expression as PfEMP1 was not detectable on the surface of cells bearing chromosome 9 deletions. While it is not clear which endothelial receptors are involved, C32 cells express high levels of CD36 and low levels of ICAM 1. Melanoma cell binding assays (15) confirmed that a clone from an independent isolate with a chromosome 9 deletion did not bind to melanoma cells although its parental undeleted line did. While it was possible to increase the level of binding of this clone to ICAM 1 by selection on endothelial cells, selection on melanoma cells did not result in any increase in the level of binding. As PfEMP1 is implicated in binding to ICAM-1, this result clearly indicates that, as is the case with KAHRP which clearly has an important role in cytoadherence to C32 melanoma cells, the cytoadherence molecule may not be essential for all PfEMP1-receptor interactions.

PfEMP1 could not be detected on the surface of 3 independent chromosome 9 deletion lines although it was clearly present on the parental lines and this indicates that the chromosome 9 product is in most cases necessary for assembly of PfEMP1 on the surface, but as with KAHRP, this can be circumvented in some situations. Alternatively, the chromosome 9 product may be required for only a subset of endothelial receptor interactions.

Clone ItG2 differs from many other parasite lines in that cytoadherence is stable over many generations (22). ItG2 is an established model to study cytoadherence. Cytoadherent clones derived from ItG2 (eg. B8) possess a chromosome 9 of intermediate size (Figure 1) between that of cytoadherent isolate 1776 and its non-cytoadherent derivative clone C10 (19). This was due to a deletion of intermediate size at the right end of the chromosome, as well as an internal deletion of about 15kb which deleted an ORF at the site of the most common breakpoints in other isolates (14). The remaining segment of about 55kb is colinear with its counterpart in 3D7 and this segment, therefore, defines the cytoadherence locus on chromosome 9. As no *var* genes were detectable in this region (14), it must contain a novel cytoadherence gene.

EXAMPLE 2

Identification of *clag*9

A 55kb region at the right end of chromosome 9 has cloned in YACs and a detailed map generated (Figure 1). Technical problems caused by the high AT content of *P. falciparum* DNA were eventually overcome by using long PCR (21) with low temperature (60°) extensions (10) to amplify individual segments from this region. Segments of up to 16 kb have been amplified using primers derived from sequence tag sites mapped to this region. These individual fragments cover the entire 55 kb region containing the putative cytoadherence locus. Subclones were generated from *Dra* I and *Rsa* I fragments of these long PCR products to facilitate sequencing. This region is sequenced using a YAC clone referred to as YAC1039.

The sequence revealed a prime candidate gene: it is located just distal to the common breakpoint and at least five exons were intially demonstrated within a region of at least 7 kb. The exons and introns were initially distinguished by the considerably higher AT content of the introns and the open reading frames of the exons. These predictions were then tested by RT-PCR from mRNA prepared from gelatin-purified trophozoite stage parasites of clone 3D7. The PCR products, of which one example is shown (Figure 2), were clearly of the sizes expected for the spliced products rather than the genomic size. The inventors confirmed this by sequencing the RT-PCR products across each splice junction found. The inventors conclude that this gene is expressed in *P. falciparum* clone 3D7 and further sequencing of genomic DNA showed that there are a

total of 9 exons. This is shown in Fig 1.

The gene was named the cytoadherence-linked asexual gene (*clag*). As there are a number of *clag* genes in the genome of *P.falciparum,* the nomenclature adopted by the inventors is to attach the number of the chromosome of origin and where necessary when more than one gene is present on a chromosome, a dot number. The nucleotide sequence and corresponding amino acid sequence of *clag9* is represented in <400>1 and <400>2, respectively. Other *clag* genes, *clag3.1, clag3.2* and *clag2,* encode amino acid sequences set forth in <400>11, 12 and 13, respectively.

A hydrophobicity plot generated by the program TopPred II predicts several potential transmembrane domains in the protein CLAG9 (Figure 3). The prediction indicated with certainty that four of these domains are localized in a membrane, presumably that of the red cell.

Southern hybridization to *Hind* III fragments of DNA from a number of *P. falciparum* isolates and clones revealed two hybridizing fragments (expected because there is an internal *Hind* III site) of 4kb and 8.5kb present in isolates/clones with an intact chromosome 9 (CSL2 and 3D7) and in ItG2 clone B8 but absent from those clones (D10, E12, C10, NF7, 7G8) with large chromosome 9 deletions. Pulsed field electrophoresis confirmed that *clag9* was located on chromosome 9. Further, *clag9* could be amplified by PCR using YACs 773 and 1039 as templates. As these have been mapped on chromosome 9 in detail (14), there can be no doubt that *clag9* is located in the deletable region of chromosome 9. This is confirmed by sequencing of YAC 1039. *clag9* is transcribed in ItG2 clone B8.

EXAMPLE 3

Inhibition of C32 melanoma binding by an antisense construct of *clag*

In order to examine whether *clag9* function was required for cytoadherence to melanoma cells, the inventors generated an antisense construct HC.ASC1, consisting of two exons of *clag9* in vector HC 1 (16) (Figure 4). In this construct, the *clag9* exons are inserted in the 3'-5' orientation, 3' to the powerful calmodulin promoter and so it would be expected that anti-*clag9*

RNA would be expressed at a high level in transfectants. HC.ASC1 was electroporated into stably cytoadherent *P. falciparum* clone 3D7 under the conditions described (17, 23) and the cells were cultured for 10 weeks in 0.1mM pyrimethamine.

The resulting pyrimethamine-resistant line 3D7.HC.ASC1 was tested for cytoadherence to C32 melanoma cells after 10 weeks of culture. In duplicate experiments it initially showed 3 fold lower binding to melanoma cells than did the parental clone 3D7 (Table 3). Over the next four weeks binding decreased to 15 fold lower, using 3D7 transfected with an unrelated recombinant HC 7 at the same time as HC.ASC1 and cultured in parallel as the control (Table 3). This is consistent with the hypothesis that *clag9* is essential for cytoadherence to C32 melanoma cells.

Line 3D7.HC.ASC1 was tested by PCR to examine whether it had integrated into the *clag9* gene in order to distinguish between a targeted gene disruption or inhibition due to antisense RNA production. These reactions demonstrated the presence of HC.ASC1and the presence of an intact chromosomal *clag9* gene (Figure 4). However a test for homologous recombination between a region of *clag 9 5'* to that included in HC.ASC1 and the HC 1 vector was negative (Figure 4). As these PCR reactions were carried out on DNA prepared from 3D7.HC.ASC1 at weeks 9 and 15 weeks of culture, the inventors conclude that it had not integrated during the course of these experiments but continued replicating as an episome.

To confirm that the lowered binding was determined by the presence of the plasmid expressing antisense-*clag9* RNA, we cultured 3D7.HC.ASC1 in the absence of pyrimethamine for several weeks after the first experiment shown in Table 3. Under these conditions it has been demonstrated that the plasmid, and, hence, pyrimethamine resistance, is lost, unless it has integrated into the chromosome. After 4 weeks the line so-obtained, 3D7.HC.ASC1p$^-$ exhibited 2.7 fold greater binding to melanoma cells than 3D7.HC.ASC1 cultured throughout this time in pyrimethamine (Table 3) while after 7 weeks without pyrimethamine it had regained full binding ability (Table 3). This result strongly supports the conclusion that the presence of plasmid HC.ASC1 rather than some unrelated change such as *var* gene switching in the parasite line is responsible for the change in phenotype. It would appear that loss of all copies of the plasmid from all cells took more than 4 weeks.

Southern blotting of the 3D7.HC.ASC1 with a *clag9* sequence present in the construct revealed a very high copy number (at least 100x the chromosomal intensity of *clag9* in 3D7) while hybridization with a *clag9* sequence not present in the construct revealed that the BglII site of the plasmid had not been introduced into *clag9* (Fig5).

One possibility was that 3D7.HC.ASC1 had undergone a subtelomeric deletion of chromosome 2 and that the loss of ability to bind was due to its conversion to a knobless phenotype by a chromosome 2 deletion (5). This was highly unlikely as a gelatin separation was always employed before binding was measured, and it has been established that this selects for cells with knobs (24). Furthermore, the KAHRP gene was present as determined by PCR. In order to confirm that 3D7.HC.ASC1 continued to produce knobs it was examined by transmission electron microscopy. All 3D7.HC.ASC1 cells examined had characteristic electron-dense knobs whereas these were not present in the knobless control B8.

EXAMPLE 4

Inhibition of Melanoma Binding by a Targeted Gene Disruption of *clag* in Clone 3D7

The inventors generated a construct of *clag* suitable for a TGD (Figure 6). It consisted of an incomplete copy of *clag9* cloned in plasmid pTgD-TS.C5/H3 (23) and was designated pAC4.CLAG. It was electroporated into *P. falciparum* isolate 3D7 under the conditions described (17) and cultured for 3 weeks in 0.1mM pyrimethamine. Pyrimethamine was then withdrawn for 3 weeks to allow loss of the plasmid. This cycle was repeated twice more. Cells into which the plasmid had become integrated were then selected by exposure again to pyrimethamine for 3 weeks.

To examine whether homologous recombination had in fact occurred a PCR test was employed. This relied on sequences in the chromosomal copy of *clag9* which were outside, either 3' or 5', to the segment of *clag9* included in pAC4.CLAG. Primers located in these regions together with primers located in vector regions could only amplify the predicted regions of DNA if pAC4.CLAG had inserted into chromosome 9 *via* recombination with *clag9*. Both the 5' and 3' primer sets generated fragments of sizes consistent with integration (Figure 6), but only after 18

weeks of culture. As this event must have produced two incomplete copies of the gene, a targeted gene disruption has been produced.

Cells in this uncloned mixture were then tested for cytoadherence to melanoma cells. They bound 10-20-fold less than 3D7 when assayed simultaneously (Table 3). Furthermore they showed considerably lower binding to purified CD36 in the one experiment conducted to date (30 cf 120 cells/30 fields). Transmission electron microscopy revealed that all cells examined continued to express knobs.

Clones were generated and one particular clone, 11E, studied in depth. 11E shows only background levels of binding to melanoma cells. Southern blotting of a pulsed field gel after BglII digestion demonstrated that the BglII site of the plasmid had in fact been introduced into *clag9* as shown by the much smaller BglII fragment in Fig5. Attempts to increase the level of binding of clone 11E to melanoma cells by upselection failed. As well, the inventors carried out an independent knockout with a distinguishable insert and obtained the same phenotype (Table 3): it shows a binding level to purified CD36 which is 60 times lower than that of the parental line 3D7.

EXAMPLE 5

Cellular Location of CLAG9

The inventors purified pGEX fused polypeptides corresponding to 6 different regions of *clag9*. These correspond to sequences on either side of two of the hydrophobic regions and so if CLAG9 does indeed traverse the red cell membrane, at least two of these sequences should be on the outside and be detectable by immunofluorescence (Figure 7) and/or agglutination of the unfixed cells. The affinity purification procedure widely used for pGex fusions resulted in considerable degradation. The purification procedures as modified utilising ion exchange chromatography which avoided the degradation problem and preparations are now used for rabbit antibody preparation.

Antibodies to 3 chemically synthesized peptides <400>14, <400>15 and <400>16 were prepared

and antibodies raised to them in rabbits as described in Example 5.

Results obtained demonstrate that CLAG9 is in the extra-parasite space rather than confined to the parasite.

EXAMPLE 6

Antibodies to CLAG9 Synthetic Peptides

Three 16 mer synthetic peptides derived from the translated *clag9* nucleotide sequence were synthesised. Each peptide contained 15 CLAG9 amino acid residues plus a single cystine residue at the amino terminal end to facilitate coupling to carrier protein. Peptide 1 corresponds to the CLAG9 amino acid sequence RKYISIYLLEELEKL <400>14 comprising residues 650-664. Peptide 2 corresponds to the CLAG9 amino acid sequence SIDWQVGYAISHGLS <400>15 comprising residues 1160-1174. Peptide 3 corresponds to the CLAG9 amino acid sequence SHRRNDDVSMNNIFM <400>16 comprising residues 910-924.

For each peptide two rabbits were injected intramuscularly with 300 μg of peptide which had been conjugated to diphtheria toxoid as a carrier protein. The initial dose was given as 1:1 emulsion with Freund's Complete Adjuvant and the 4 subsequent doses, each of 300ug, given in conjunction with Freund's Incomplete Adjuvant. Doses were spaced at 3 weekly intervals. Pre-bleed bloods were collected from each rabbit before immunization commenced. Final Test Bleed's were collected after the 5th immunization.

ELISA assay's were carried out using pre-bleed and Final Test Bleed rabbit sera from all the rabbits immunized with the peptides. ELISA assays were performed in 96 well immuno-assay plates. Peptides 1-3 were bound separately to individual plates for 16 hours at 4^{0}C in carbonate buffer. The trays were then blocked by 5% w/v skim-milk in Tris/NaCl buffer for 3 hours at room temperature. Rabbit Pre-Bleed and Final Test Bleed sera was diluted in the blocking buffer and added to the appropriate tray. This was incubated for 1 hour at room temperature, then washed in Tris/NaCl buffer. Anti-Rabbit IgG conjugated to Horse-radish peroxidase was added to a concentration of 1 in 1000. The trays were incubated for 1 hour at room temperature. The trays

were again washed in Tris/NaCl buffer and 2'2-azino-di[3-ethylbenzthiazoline sulfonate] and H_2O_2 added. The resulting colour reaction was read in a spectrophotometer at 405nm wavelength.

For peptide 1 one rabbit showed no detectable immune response to the peptide. The second rabbit had an ELISA titre of > 1:2000. For peptide 2 both rabbits showed detectable immune responses to the peptide. The first rabbit had an ELISA titre of between 1:1000 and 1:2000. The second rabbit had an ELISA titre of > 1:2000. For peptide 3 one rabbit showed no detectable immune response to the peptide. The second rabbit had an ELISA titre of > 1:2000. No rabbit sera showed detectable immune responses to any peptide in the Pre Bleed samples.

The antibodies may be used, for example, in immunoflorescence analysis to determine expression patterns of the *clag* genes. One example of immunoflorescence is shown in Figure 7. This figure shows the staining pattern produced on acetone fixed film of *P. falciparum* trophozoites by antibodies to CLAG9 peptide 3 (<400>16).

EXAMPLE 7

Clag9 is a member of a gene family

Nucleotide sequences of a 60-70% similarity to *clag9* were observed on chromosomes 1, 2, 3 and 4. After aligning the sequences, a hybridization probe was designed to a relatively conserved region. This hybridized at low stringency to at least 9 of the chromosomes separated by pulsed field electrophoresis (Fig. 8). Hence, the *clag* gene family has at least 9 members. As the *clag*9 knockout did not retain the ability to cytoadhere to CD36, it is likely that they are not homologues that carry out the same function. It is proposed, therefore, that they are paralogues with related functions.

The complete sequences of the 2 *clag* genes on chromosome 3 *(clag3.1* and *clag3.2)* of *P.falciparum* clone 3D7 have been determined as has the complete sequence of a single *clag* gene on chromosome 2 *(clag2).* Fragments of other sequences from chromosomes 1, 4,11 and 13 have also been identified. The complete sequences all have the same predicted splicing pattern.

clag9 has the same pattern of 9 exons. The arrangement of hydrophobic regions also appears to be substantially the same (Fig 9).

The degree of homology varies widely. *clags*3.1 and 3.2 appear to result from a duplication and it is possible that *clag3.2* is an inactive pseudogene as it does not appear to be expressed in red blood cells whereas *clag3.1* and *clag2* are. Alternatively, this may be an example of a *clag* that is expressed elsewhere in the life cycle. A number of *clag3* cDNA and genomic clones were sequenced and this established that only *clag3.1* was expressed. An amino acid sequence alignment for all current completed amino acid sequences is shown in Fig 9.

The inventors have established that *clag3.1* is expressed in blood stages of 3D7 since they demonstrated the presence of spliced mRNA by RT-PCR. This is also the case for line Dd2 since the inventors found an almost identical sequence in an EST (ie. cDNA) database. *Clags* 2, 3.1 and 3.2 are all located between 100-150kb from one end of the chromosome, a similar location to that of *clag9*. It is notable that the majority of malaria genes which encode products that are transported out to the red cell or its surface are located in such recombinationally active regions. Examples are *var* (PfEMP1), STEVOR, PfEMPIII, KAHRP, RESA, FIRA, and HRPIII.

On the other hand, the fact that the cDNA from Dd2 is almost identical to *clag3*, and a fragmentary cDNA sequence from isolate 1916 is identical to that of *clag*9, suggest that the *clag* family may have diverged long ago and individual members are now highly conserved. This is supported by the fact that the *Hind*III fragments of *clag*9 were identical in the three totally independent isolates.

The nucleotide sequence for *clag3.1* and *clag3.2* is shown in accession number Z97348 of GenBank. *Clag2* is shown under accession number AE001428.

EXAMPLE 8

CLAG and PfEMP1

A number of molecules are involved in cytoadherence, either individually or in combination although the way in which these molecules interact is not well understood. PfEMP1 is generally

thought to be of major importance in binding to the cell adhesion molecule CD36. However, red cells containing parasites which do not have a functional *clag*9 gene and which are not able to bind to CD36 still express PfEMP1 on their surface, bringing into question the role of PfEMP1 as the omnipotent ligand for CD36.

The inventors carried out a series of experiments in which trophozoite stage parasites from the parental line 3D7 (which has a functional *clag*9 gene) and from the TGD clone 11E (which does not have a functional *clag*9 gene) were surface labelled with ^{125}Iodine. The samples were then divided into two and half of each was subjected to trypsinisation. PfEMP1 is rapidly cleaved from the red cell surface by mild trypsinization. All samples were then extracted sequentially with Triton X-100 followed by SDS. PfEMP1 is soluble in sodium dodecyl sulphate (SDS) but not in Triton X-100. I^{125}- SDS extracts were fractionated on an SDS -PAGE gel and the resulting autoradiograph showed strong bands of the correct size for PfEMP1 in lanes containing 3D7 and 11E parasite extracts (Fig. 10). Furthermore the intensity of these bands was reduced dramatically for trypsin treated parasite extracts. This indicates that a molecule of the same size and exhibiting the same characteristics as PfEMP1 is expressed on the surface of 3D7 and 3D7 TGD parasitised RBC's.

In a second experiment, samples of trophozoite stage parasites of lines 3D7, clone 11E and unrelated clone C10 (which has a short chromosome 9 and is known not to express PfEMP1) were divided into two and half of each was subjected to trypsinisation followed by sequential extraction with Triton X-100 and SDS. Following SDS fractionation and transfer to nylon membrane, blots were probed with an antibody to the internal domain of PfEMP1. As expected, no bands were visible in lanes containing C10 parasite extracts; however strong bands were seen with untrypsinised 3D7 and 11E parasites and these showed greatly reduced intensity in lanes containing trypsinised parasite extracts. This surprisingly shows that PfEMP1 is still expressed on the surface of clag9 TGD parasites. One possible interpretation is that a truncated CLAG9 is expressed and is sufficient to maintain PfEMP1 on the surface. Another is that there is a second relevant gene in the deleted region.

EXAMPLE 9

Stages of the life cycle where *clag* paralogues might function

One inference is that the role of *clag* genes in cytoadherence may be in determining, together with *var*, receptor-binding specificity. Alternatively, a *clag* paralogue could be one or more of the receptor-parasite ligand interactions which occur in the mosquito host, such as adherence of the ookinete to the midgut lumen or invasion of salivary gland cells by sporozoites. It is further possible that a *clag* paralogue is involved in binding of merozoites to red cells. If this latter model is correct and a chemotherapeutic that inhibited an active site common to all *clag* paralogues could be found, then simultaneous mutations in a number of paralogues would be required in order for drug resistance to develop.

EXAMPLE 10

Cellular locations of proteins of the CLAG family

Agglutination, indirect fluorescent antibody staining and immunoelectron microscopy are used to determine the cellular locations of CLAG paralogues. The patterns of reactivity with human sera are also determined.

*clag*9 has been successfully expressed as a series of fragments fused to glutathione S-transferase using vector pGEX 2T. As hydrophobic domains can be difficult to express, *clag* cDNA is amplified by PCR, fragmented by sonication and fragments of greater than 300bp are inserted into the SmaI site of pGEX 2T. A large number of colonies are screened for production of abundant fused polypeptides by PAGE and several where isolated. Sequence runs establish which segment is encoded in each and this allowed the selection of representative clones from each region. Fused polypeptides were prepared from clones corresponding to each domain of CLAG by ion exchange chromatography and are being used for production of rabbit antibodies.

The information derived from this should allows the design of constructs of the *clag* paralogues bounded at points precisely equivalent to those which in *clag*9 results in stable soluble pGEX fused polypeptides. If *clag*9 indeed traverses the red cell membrane, antibodies to external

domains should agglutinate the cells and should react with intact infected cells by indirect immunofluorescence.

The generation of antibodies specific for individual *clag* paralogues permits the use of a variety of approaches to examine questions about the expression of *clag* paralogues at the single cell level. While it is clear that 3D7 expresses *clag* 2, 3.1 and 9 mRNAs, this does not necessarily mean that every parasite in the culture expresses both. Two-color immunofluorescent studies (25) can be used to establish whether both CLAG9 and CLAG3 are present in the same cells. This approach is extended in pairwise-fashion to other paralogues as antibodies become available.

	Expt 1 (6 weeks)		Expt 2 (7 weeks)		Expt 3 (10 weeks)		Expt 4 (16 weeks)		Expt 5 (17 weeks)		Expt 6	
3D7.HC.ASC1	35	37	19	16	8	11	8	6				
3D7.HC.ASC1p.					24	28	142	148				
3D7.HC 7					144	138						
3D7	110	105	192	183			189	153	192	183	145	148
3D7.Pac4 Clag									8	21		
Clone 3D7.11E											8	12

TABLE 3. Inhibition of cytoadherence to melanoma cells after transfection of 3D7 with antisense construct HC.ASC1 and knockout vector Pac4 Clag. *falciparum* clone 3D7 was electroporated with Pac4 Clag, HC.ASC1 or HC 7 (transfection control) and cultured in 0.1mM pyrimethamine. Once a targeted gene disruption of clag had been confirmed by Southern blotting the transfected line 3D7.Pac4 Clag was cloned After synchronization by gelatin flotation, parasites were grown to 5-8% parasitaemia and cytoadherence to melanoma cells was then measured as described [10]. Results are shown as parasitized cells bound per 100 melanoma cells. Duplicates are shown for each point.

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CLAIMS:

1. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a protein which is involved in, associated with or which otherwise facilitates host cells parasitized with a *Plasmodium* species cytoadhering to other cells.

2. An isolated nucleic acid molecule according to claim 1 wherein the parasitized cells are red blood cells.

3. An isolated nucleic acid molecule according to claim 2 wherein the *Plasmodium* species is *Plasmodium falciparum.*

4. An isolated nucleic acid molecule according to any one of claims 1 to 3 which encodes a product which:

(i) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to C32 melanoma cells;

(ii) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to endothelial cells;

(iii) is capable of binding or otherwise interacting with purified CD36;

(iv) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to endothelial cells at a particular life cycle stage; and/or

(v) is capable of interacting with the PfEMP1-KAHRP complex with the proviso that the product is not PfEMP1.

5. A nucleic acid molecule according to claim 4 comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in <400>2 or an amino acid sequence having at least about 35% similarity to all or 20 contiguous amino acids thereof.

6. A nucleic acid molecule according to claim 4 comprising a nucleotide sequence encoding

an amino acid sequence substantially as set forth in <400>11 or an amino acid sequence having at least about 35% similarity to all or at least about 20 contiguous amino acids thereof.

7. A nucleic acid molecule according to claim 4 comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in <400>12 or an amino acid sequence having at least about 35% similarity to all or at least about 20 contiguous amino acids thereof.

8. A nucleic acid molecule according to claim 4 comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in <400>13 or an amino acid sequence having at least about 35% similarity to all or at least about 20 contiguous amino acids thereof.

9. A nucleic acid molecule according to claim 4 comprising a nucleotide sequence substantially as set forth in <400>1 or a nucleotide sequence having at least about 35% similarity to all or at least about 60 contiguous nucleotides thereof or a nucleotide sequence capable of hybridising to <400>1 under low stringency conditions.

10. An isolated nucleic acid molecule comprising a nucleotide sequence which:

(i) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to C32 melanoma cells;

(ii) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to endothelial cells;

(iii) encodes a product capable of binding or otherwise interacting with CD36;

(iv) encodes a product capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to endothelial cells at a particular life cycle stage;

(v) encodes a product capable of interacting with PfEMP1-KAHRP complex but is not PfEMP1;

(vi) comprises a nucleotide sequence substantially as set forth in <400>1 or a nucleotide sequence having at least about 35% similarity to <400>1 and/or is capable of hybridising to <400>1 under low stringency conditions; and/or

(vii) encodes a product comprising an amount and sequence substantially as set forth in

<400>2 or <400>11 or <400>12 or <400>13 or an amino acid sequence having at least 30% similarity thereto.

11. An isolated protein comprising a sequence of amino acids which protein is involved in, associated with or which otherwise facilitates host cells parasitized with a *Plasmodium* species cytoadhering to other cells.

12. An isolated protein according to claim 11 wherein the parasitized cells are red blood cells.

13. An isolated protein according to claim 12 wherein the *Plasmodium* species is *Plasmodium falciparum.*

14. An isolated protein according to any one of claims 11 to 13 which:

(i) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to C32 melanoma cells;

(ii) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to endothelial cells;

(iii) is capable of binding or otherwise interacting with purified CD36;

(iv) facilitates red blood cells parasitized with *Plasmodium* species cytoadhering to endothelial cells at a particular life cycle stage; and/or

(v) is capable of interacting with the PfEMP1-KAHRP complex with the proviso that the molecule is not PfEMP1.

15. An isolated protein according to claim 14 comprising an amino acid sequence substantially as set forth in <400>2 or an amino acid sequence having at least about 35% similarity to all or at least about 20 contiguous amino acids thereof.

16. An isolated protein according to claim 14 comprising an amino acid sequence substantially as set forth in <400>11 or an amino acid sequence having at least about 35%

similarity to all or at least about 20 contiguous amino acids thereof.

17. An isolated protein according to claim 14 comprising an amino acid sequence substantially as set forth in <400>12 or an amino acid sequence having at least about 35% similarity to all or at least about 20 contiguous amino acids thereof.

18. An isolated protein according to claim 14 comprising a nucleotide sequence encoding an amino acid sequence substantially as set forth in <400>13 or an amino acid sequence having at least about 35% similarity to all or at least about 20 contiguous amino acids thereof.

19. An isolated protein according to claim 14 encoded by a nucleotide sequence substantially as set forth in <400>1 or a nucleotide sequence having at least 35% similarity to all or at least about 60 contiguous nucleotides thereof or a nucleotide sequence capable of hybridising to <400>1 under low stringency conditions.

20. An isolated protein which:

(i) is capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to C32 melanoma cells;

(ii) is capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to endothelial cells;

(iii) is capable of binding or otherwise interacting with CD36;

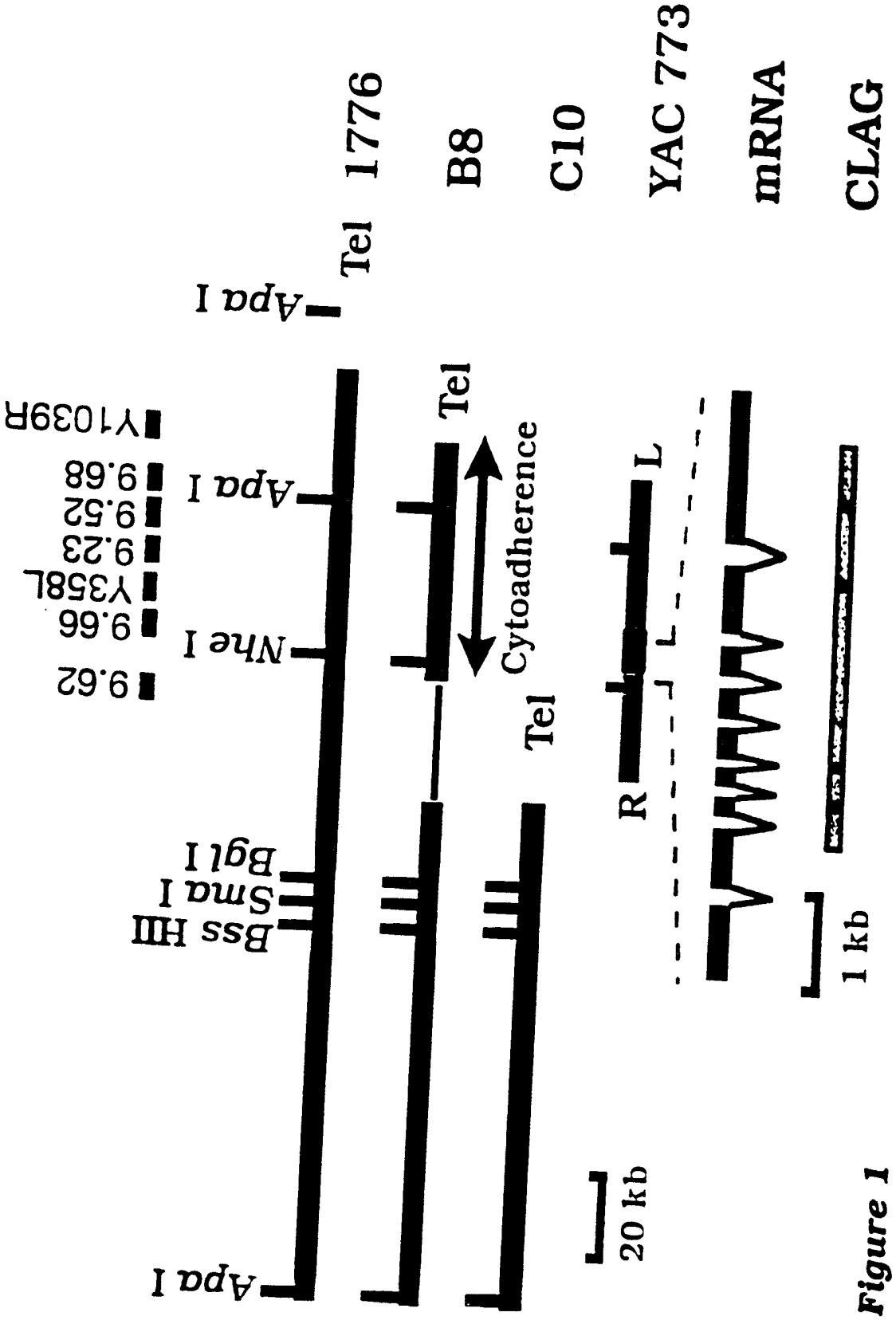
(iv) is capable of facilitating cytoadherence of *Plasmodium* sp parasitized red blood cells to endothelial cells at a particular life cycle stage;

(v) is capable of interacting with PfEMP1-KAHRP complex but is not PfEMP1;

(vi) is encoded by a nucleotide sequence substantially as set forth in <400>1 or a nucleotide sequence having at least about 35% similarity to <400>1 and/or is capable of hybridising to <400>1 under low stringency conditions; and/or

(vii) comprises an amino acid sequence substantially as set forth in <400>2 or <400>11 or <400>12 or <400>13 or an amino acid sequence having at least about 30% similarity thereto.

21. A composition comprising an antagonist of CLAG and one or more pharmaceutically acceptable carriers and/or diluents.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B8
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YAC 773
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Apa I
Tel
Cytoadherence
Tel
L
L
R
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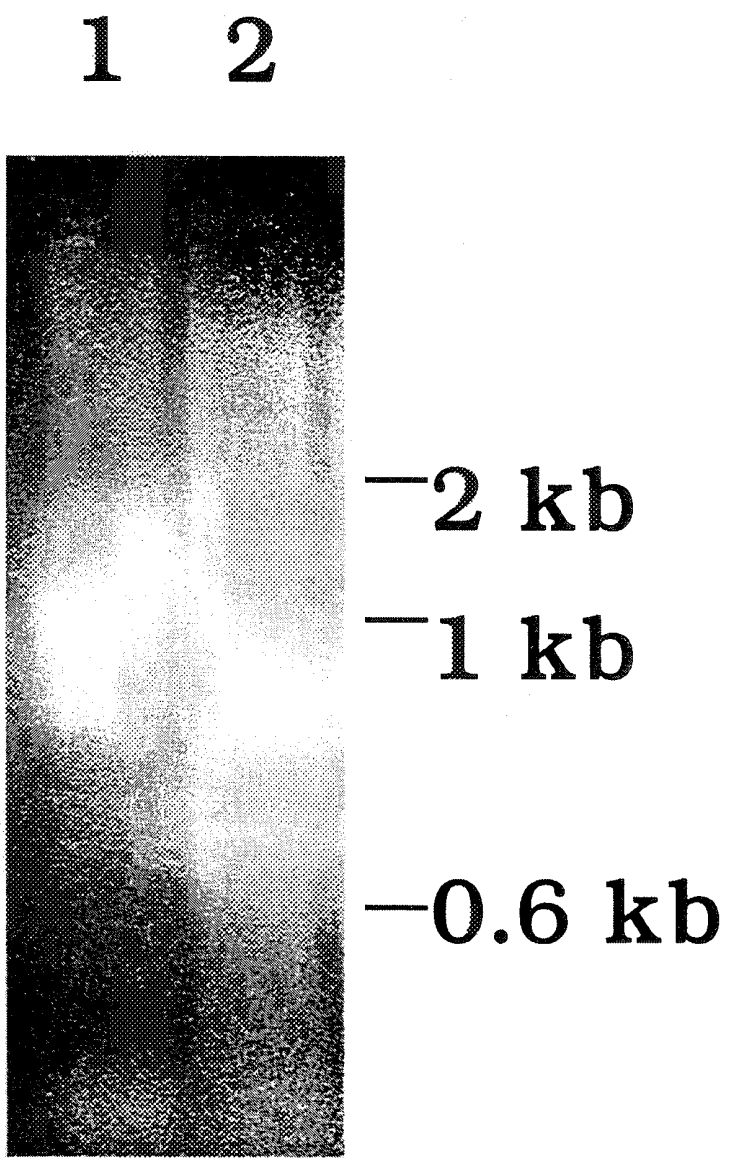
Apa I
9.52
9.23
Y358L
9.66
Nhe I
9.62
Bgl I
Sma I
Bss HII
Apa I
20 kb
1 kb

Figure 1



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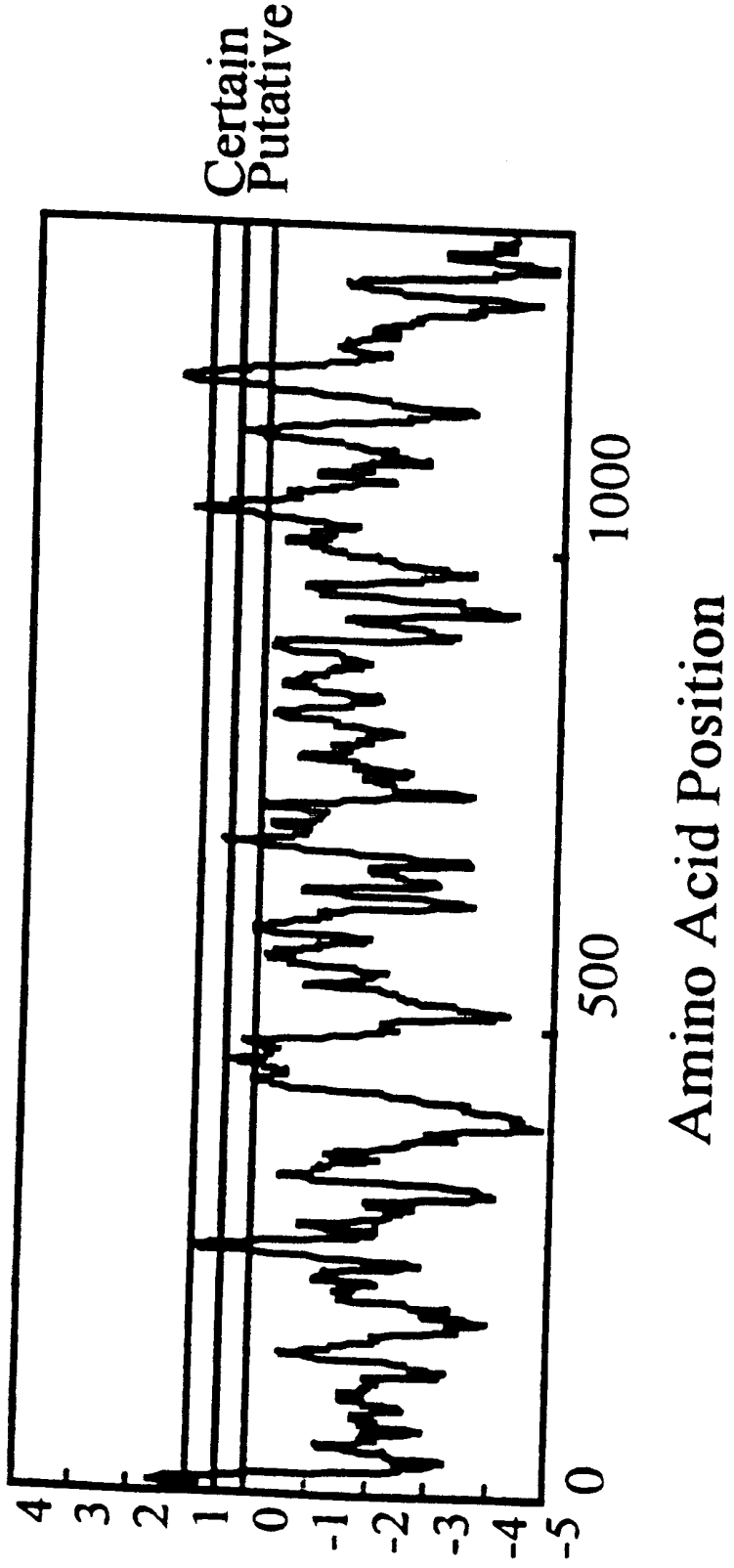
Certain Putative
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-2
-3
-4
-5
0
500
1000
Amino Acid Position

Figure 3

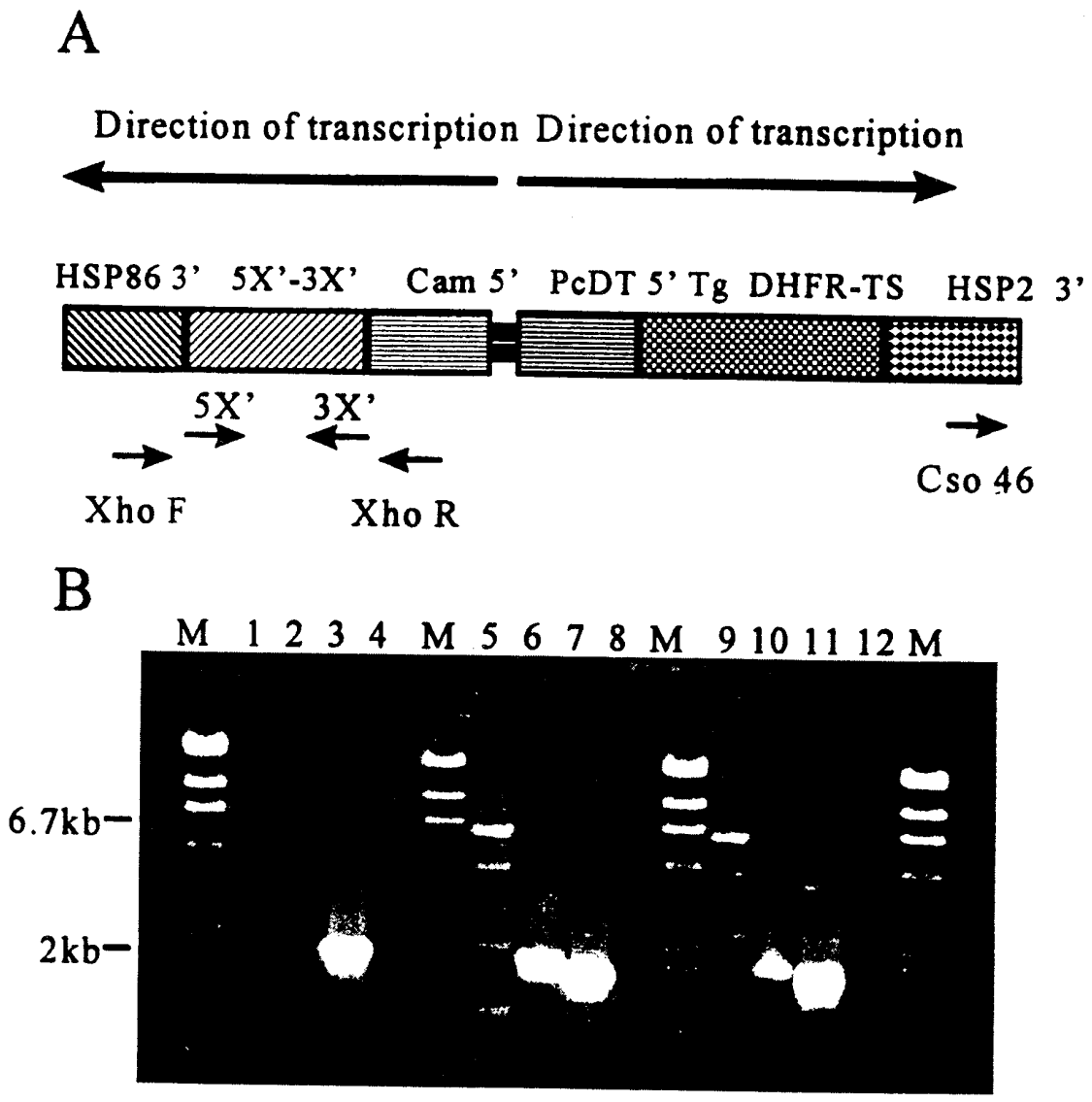
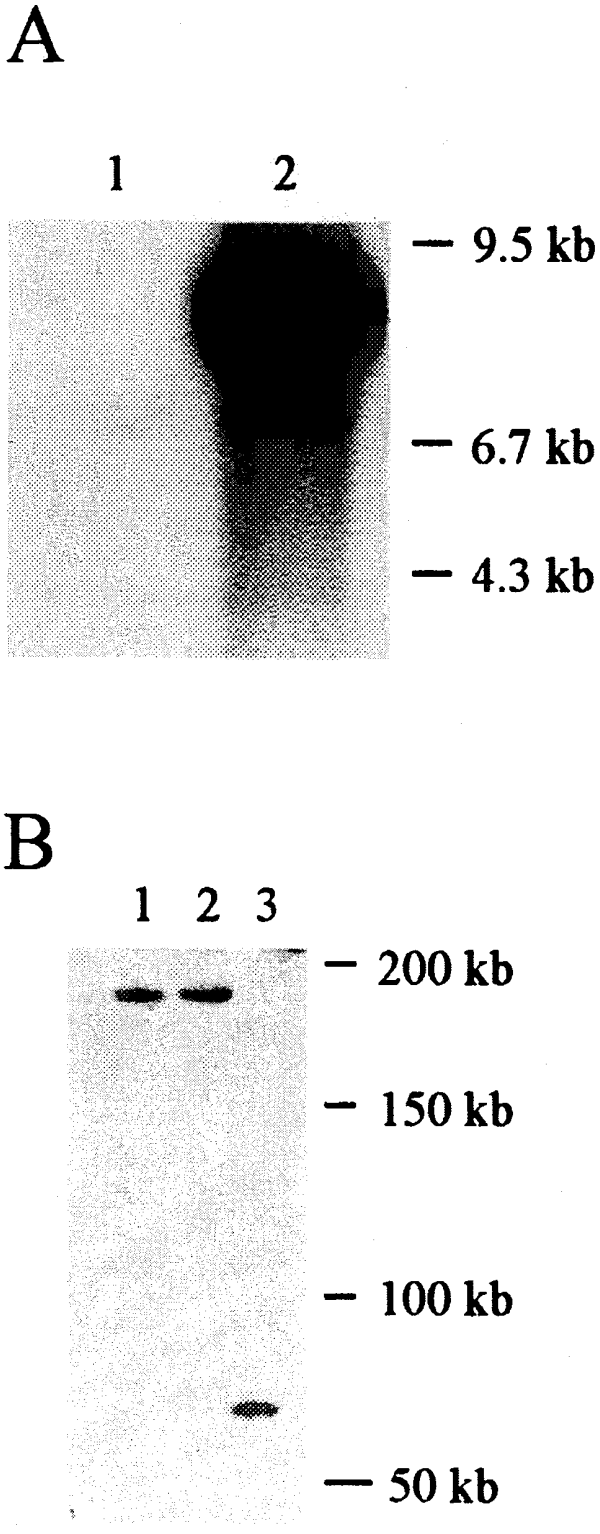

A
Direction of transcription Direction of transcription
HSP86 3' 5X'-3X' Cam 5' PcDT 5' Tg DHFR-TS HSP2 3'
5X'
3X'
Xho F
Xho R
Cso 46
B
M 1 2 3 4 M 5 6 7 8 M 9 10 11 12 M
6.7kb
2kb

Figure 4



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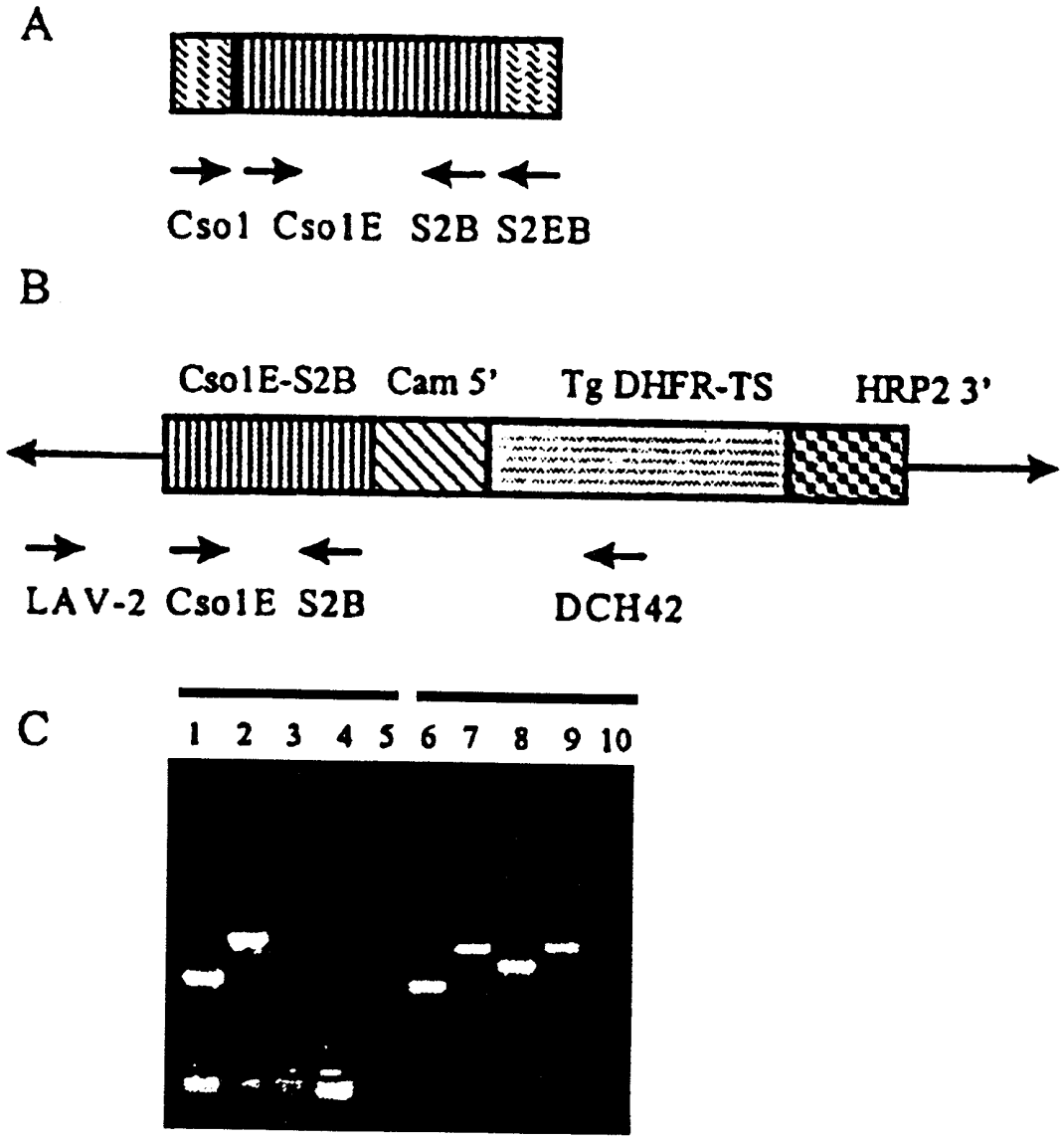
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B
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LAV-2 CsolE S2B
DCH42
C
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Figure 6

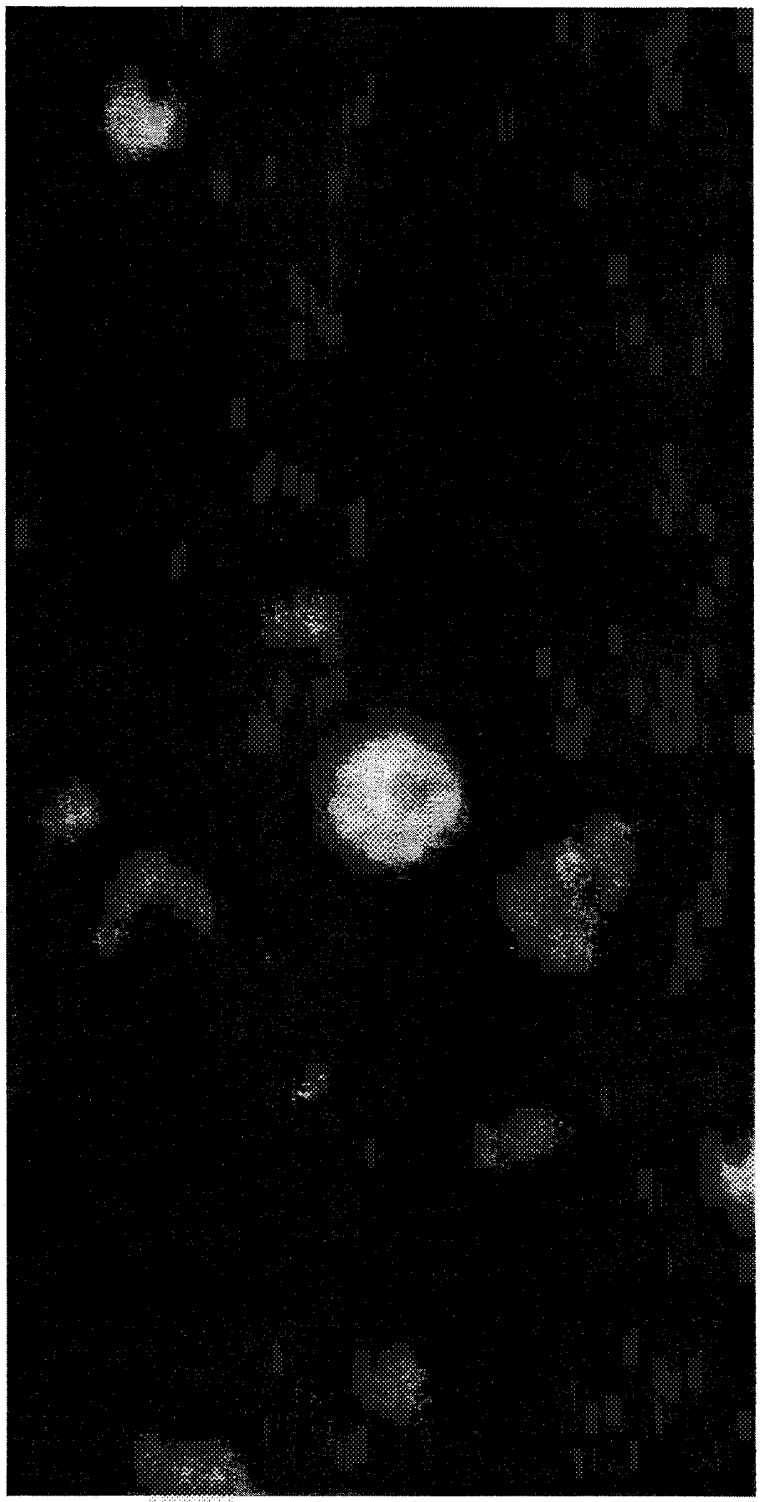


Figure 7

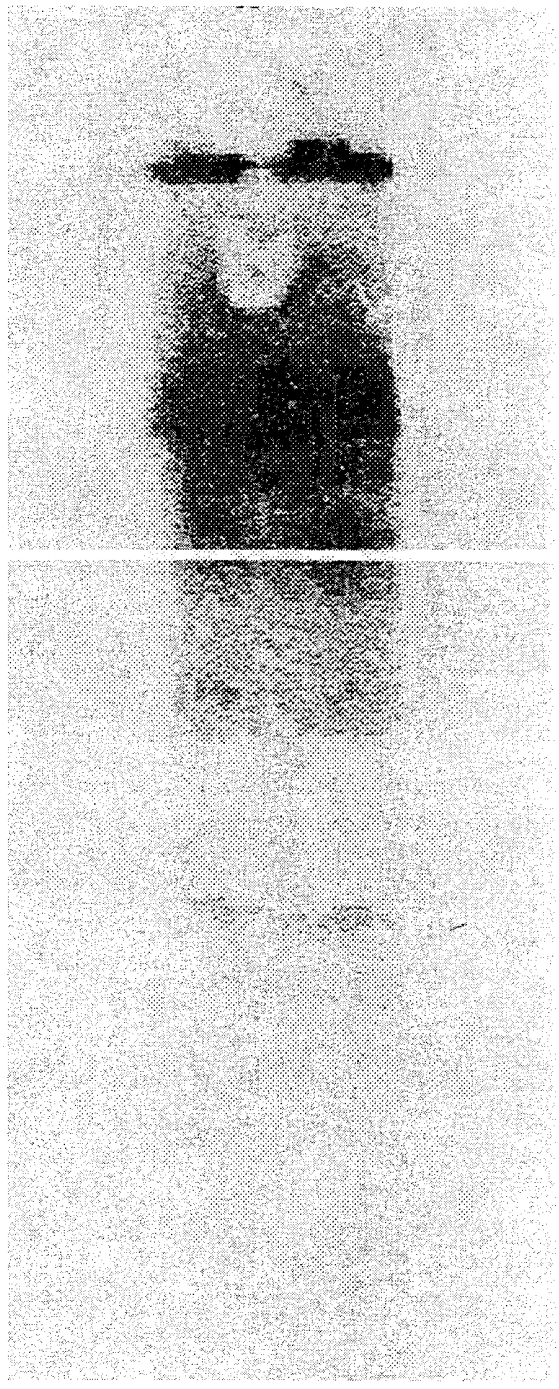


Figure 8

FIGURE 9 (I)

```
clag3.1  .......MVSF FKTPIFILII FLYLNEKVIC SINENQ.... ..........
clag3.2  .......MVSF FKTPIIIFFF LLCLNEKVLC SINENENL.. ..........
clag2.1  .......MVSS VKSSLFLLIF FLYLKKNVIC SINDNVNENI TEGLDEYEFG
clag9    .......MIIW FIQPTIFYII FILAR..NIQ CTYK...... ..........

clag3.1  .....NENDTI SQNVNQHENI NQNVNDND.. .NIEQLKSMI GNDELHKNLT
clag3.2  .....GENKNE NANVNTPENL NKLLNEYD.. .NIEQLKSMI GNDELHKNLT
clag2.1  NENINESITE NVNVNVTENE KDNLIYNDDN NNIEELKSMI GNDELHKNLS
clag9    .......... .......... ......GD.. .NINEIKSIL DNDELYNSLS

clag3.1  ILEKLILESL EKDKLKYPLL KQGTEQLIDI SKFNKKNITD ADD..ETYII
clag3.2  ILEKLILESL EKDKLKYPLL KQGTEQLIDI SKFNKKNITD ADD..ETYII
clag2.1  ILEKLILDSL KKDKLKLPLI KEGTEEYLDI SKFKKKILTD SDD..KTYIL
clag9    NLENLLLQTL EQDELKI'TM KGDLDKYLNM SNFKILNELN ADGSRKAIYN

clag3.1  PTVQSTFHDI VKYEHLIKEQ SIEIYNSDIS DKIKKKIFIV RTLKTIKLML
clag3.2  PTVQSSFHDI VKYEHLIKEQ SIEIYNSDIS DKIKKKIFIV RTLKTIKLML
clag2.1  PTLESSFYDI TKYEHILKEQ LIEEYNSKIS DAVKKKLLIV RTLKTIKLML
clag9    PTSNCSANDI VKYEHTLKTQ ITLEYKPEIS DMLKRKNIVV RTLKIIKFMQ
```

FIGURE 9 (II)

```
clag3.1 IPLNSYKQNN DLKSALEELN NVFTNKEAQE ES.SPIGDHG TFFRKLLTHV
clag3.2 IPLNSYKQNN DLKSALEELN NVFTNKEAQK ES.SPIGDHG TFFRKLLTHV
clag2.1 IPLNAYKEKN DLKIALEELN NVITHRTYET LKKSPIENPG EFFRKLLTHV
clag9   TPMSAYKNTN NIKQSLLEMN KLFTNKEK.. .KLNEHTINA LRLRDRIFNT

clag3.1 RTIKENEDIE NKGETLILGD NKIDVMNSND FFFTTNSNVK FMENLDDITN
clag3.2 RTIKENEDIE NKGETLILGD NKIDVMNSND FFFTTNSNVK FMENLDDITN
clag2.1 KEVKESKEIE NKGEYLILGN DKIEIMDAHD FFFTTNSNIK FMETLDSISN
clag9   NNLT.HRSIK KGISTYMPID TKSDIIDYDH LXFTNXPSIX LMENLDKLAN

clag3.1 QYGLGLINHL GPHLIALGHF TVLKLALKNY KNYFEAKSIK FFSWQKILEF
clag3.2 QYGLGLINHL GPHLIALGHF VVLKLALKNY KNYFEAKNIK FFSWQKILEF
clag2.1 QYGLGLINDL GPHLIALGHF MVLKLALKNY KNYFEAKNTK FFSWQKILEF
clag9   YDQRGIFNMI GSHYIAVGHF ITLKLALKNY KKYFEIGSLK YLNWQSILKF

clag3.1 SMSDRFKVLD MMCDHESVYY SEKKRRKTYL KVDRSNTSME CNILEYLLHY
clag3.2 SMSDRFKVLD MMCNHESVYY SEKKRRKTYL KVDRSSTSME CNILEYLLHY
clag2.1 SLTDRFKILD MMCDHDVVYY SQDKRRKTYL NVDTSGSSME CNILEFLIHY
clag9   NQSDRFKVLD LICDESSWYE GQMKRREQYL KNNIFSTSEE CSVLEFLIHH
```

FIGURE 9 (III)

```
clag3.1 FNKYQLEIIK TTQDTDFDLH GMMEHKYIKD YFFSFMCNDP KECIIYHTNQ
clag3.2 FNKYQLEIIK TTQDTDFDLH GMMEHKYIKD YFFSFMCNDP KECIIYHTNQ
clag2.1 FNKYQLEIIK ATQDTDFELH GMMEHKNIKD YFFSFMCNDP KECIIYHTNQ
clag9   MNKYQMELYS KMHKLSLNVQ IYLENKHLKE KFLQFMCRSR KECNIYESDR

clag3.1 FKKEANEENT FPEQ.....  ....EEPNRQI SAFNLYLNYY YFMKRYSSYG
clag3.2 FKKEANEENT FPEQ.....  ....EEPNRQI SAFNLYLNYY YFMKRYSSYG
clag2.1 FKKEAKEENT FP.....   ....EEPNREI SAYNLYLNYY YFMKRYSSYG
clag9   FKQEQEKGIE FHDNNNYKFS QENDPVSKVV DPFNLFTNYF YFIKYYSVFN

clag3.1 VKKTLYVHLL NLTGLLNYDT RAYVTSLYLP GYYNAVEMSF TEEKEFSKLF
clag3.2 TKKTLYVHLL NLTGLLNHDT RAYVTSLYLP GYYNAVEMSF TDDKEFSTLF
clag2.1 IKKTLYVHLL NLTGLLNYDT RSYVTSLYLP GYYNVVEMSF TEDVEFTTLF
clag9   SDHIIYMHLL NFVGVLNGNN NAYVSSLYLP GYYNAIQLSY KDQVGLKELY

clag3.1 ESLIQCIEKC HS..DQARQI S..KDSNLLN NIT...KCDL CKGAFLYANM
clag3.2 ESLIQCIEKC HS..DQARQI S..KDSNLLN NIT...KCDL CKGAFLYAN.
clag2.1 NNLLKCIKKC HK..EETNTN TSLMDSNSSH NYF...LHEI TKCDLLKFE.
clag9   QNLVKCVEKC YIRNRKNRSF SHRIASIFRH KKFDSSKCSI CEGTLLYIND
```

FIGURE 9 (IV)

```
clag3.1 KFDEVPSMLQ KFYVYLTKGL KIQKVSSLIK TLDIYQDYSN YLSHDINWYT
clag3.2 ....IPSMLQ KFYVYLTKGL KIQKVSSLIK TLDIYQDYSN FLSHDINWYT
clag2.1 ...EVPSMLQ KFYIYLTEGL RIQKVSFLMK TLDIYQDYSN FLSHDINWYT
clag9   QSQDKMSMAQ KFYIFVTKIL KVNNISSFIT NMNIYEDYSN YLMHDLNWYT

clag3.1 FLFLFRLTSF KEIAKKNVAE AMYLNIKDED TFNKTVVTNY WYPSPIKKYY
clag3.2 FLFLFRLTSF KEIANKNVAE AMYLNIKDED TFNKTIVTNY WYPSPIKKYY
clag2.1 FLFLFRLTSF EEISKKSVGE AMYLNIQDED SFHKTITTNY WFPSPIKKYY
clag9   FLFLFRMTTY KDIPNYSISN AMYLNIKDED DTKRTMVTFQ WMPSTIKRMH

clag3.1 TLYVRKHIPN NLVDELEKLM KSGTLEKMKK SLTFLVHVNS FLQLDFFHQL
clag3.2 TLYVRKHIPN NLVDELEKLM KSGTLEKMKK SLTFLVHVNS FLQLDFFHQL
clag2.1 TLYVRKHLPN NLLDELEKLM KSSTLEKMKK SINFLVHVNS FLQLDFFHQL
clag9   NYRIRKYISI YLLEELEKLI DNKLIEKLKK CITFLIHLNA FLQLDFFSYL

clag3.1 NEPPLGLPRS YPLSLVLEHK FKEWMNSSPA GFYFSNYQNP YIRKDLHDKV
clag3.2 NEPPLGLPRS YPLSLVLEHK FKEWMDSSPA GFYFSNYQNP YIRKDLHDKV
clag2.1 NEPPVGLPRS YPLSLILEHK FKEWMNSSPA GFYFSNYHNP YIRKELHRKV
clag9   NETPANLQHP FPISMMIEAR FKDWFIQYLT GFFFINYDDA NTRYNMPENM
```

FIGURE 9 (V)

```
clag3.1 LSQKFEPPKM NQWNKVLKSL IECAYDMYFE QRHVKNLYKY HNIYNINNKL
clag3.2 LSQKFEPPKM NQWNKVLKSL IECAYDMYFE QRHVKNLYKY HNIYNINNKL
clag2.1 LTEKFEPPKM NKWNEVLKSL IECAYDMYFE QRHVKNLYKN HNIYNINNKI
clag9   KRGTFIPPKY SKWNIHLKRF IDEAFLMYFN QKHALTLFKY HNPYNISNKI

clag3.1 MLMRDSIDLY KNNFDDVLFF ADIFNMRKYM TATPVYKKVK DRVYHTLHSI
clag3.2 MLMRDSIDLY KNNFDDVLFF ADIFNMRKYM TATPVYKKVK DRVYHTLHSI
clag2.1 MLMRDSVDLY KKNFKDVIFF ADIFNLRKYL TATPLIKKTW DRMYYFIYRN
clag9   MLMRDTFELY TKNYDQLIFG ADIMLLRKTF SCTPMSTKVW DRVKYYLHNI

clag3.1 TGNSVNFYKY GIIYGFKVNK EILKEVVDEL YSIYNFNTDI FTDTSFLQTV
clag3.2 TGNSVNFYKY GIIYGFKVNK EILKEVVDEL YSIYNFNTDI FTDTSFLQTV
clag2.1 TGNSVNFYKY GIIYGFKINK VYLKEVVDEL YSIYNFNTDI FSDTSFLQTV
clag9   IGNPINFYKH GLIYAYTINK AMLKEVVNDF FVIYKMNKDL FSETSFLQTV

clag3.1 YLLFRRIEET YRTQRRDDKI SVNNVFFMNV ANNYSKLNKE EREIEIHNSM
clag3.2 YLLFRRIEET YRTQRRDDKI SVNNVFFMNV ANNYSKLNKE EREIEIHNSM
clag2.1 YLLFRKIEDS YRTHRRNDHI GVNNIFFMNV ANNYSKLNNE EREMEIHNSM
clag9   YLLFKKIQGT YFSHRRNDDV SMNNIFMFNV EKNYSKMSQA DREKKSMNLW
```

FIGURE 9 (VI)

```
clag3.1 ASRYYAKTMF AAFQMLFSTM LSNNVDNLDK AYGLSENIQV ATSTSAFLTF
clag3.2 ASRYYAKTMF AAFQMLFSTM LSNNVDNLDK AYGLSENIQV ATSTSAFLTF
clag2.1 ASRYYSKTMF AAFQMLFSTM LSNDANNLDK VYGKSSNIQV ATSTTAFLTF
clag9   HPDFLQKNLF TVFQNDVVIQ ISNEVDKLDR IYGKADMLRL SVHDEPFLRF

clag3.1 AYVYNGSIMD SVTNSLLPPY AKKPITQLKY GKTFVFSNYF MLASKMYDML
clag3.2 AYVYNGSIMD SVTNSLLPPY AKKPITQLKY GKTFVFSNYF MLASKMYDML
clag2.1 AYVYNGSIMD SLTNRLLPPY AKKPITQLKY GKTFVFSNYF MLASQIYEML
clag9   AYAYYGSMYD KLTNVFFPMN IKKPTIQLKY GKTFIMANLY YLCSVLFSMY

clag3.1 NYKNLSLLCE YQAVASANFY SAKKVGQFLG RKFLPITTYF LVMRISWTHA
clag3.2 NYKNLSLLCE YQAVASANFY SAKKVGQFLG RKFLPITTYF LVMRISWTHA
clag2.1 NYKNLSLLCE YQAVASANYY SAKKLGQFVG RKYFPLTTYY LSLRIRASYG
clag9   NLNNXGLLCE YQAIGSANFH SYKKMSQFID KKFIPLVFYT LKERTEGIIG

clag3.1 FTTGQHLISA FGSPSSTANG KSNASGYKSP ESFFFTHGLA AEASKYLFFY
clag3.2 FTTGQHLICA FD.PKRCTPD CKNSTSYKSP Q..SFFYGWP PSSETYLFFY
clag2.1 WVHGTETKIC NS........ EGVSCSRKGP TPGKFFFNWK SDAPIYLYFY
clag9   KEWYKMVLND FD........ .....GKSMA N.......TWP .....YFGYY
```

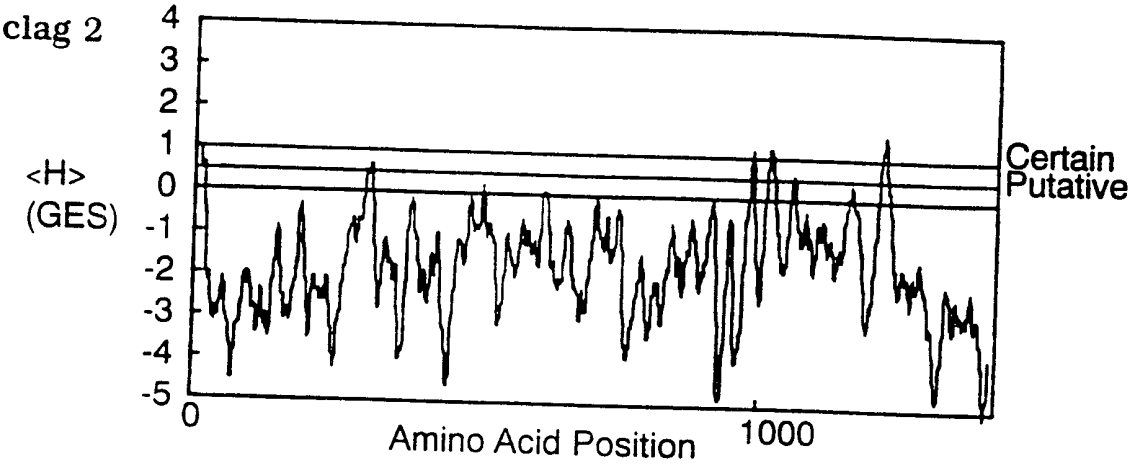
FIGURE 9 (VII)

```
clag3.1 FFTNLYLDAY KSFPGGFGPA IKEQTQHVQE QTYERKPSVH SFNRNFFMEL
clag3.2 FFTNLYLDAY KSFPGGFGPA IKEQTQHVQE QTYERKPSVH SFNRNFFMEL
clag2.1 FFSNLYLDSA KYFPGGFSTS LKEQTEHVSQ KGFKKKPMVH ELTKNLILDV
clag9   MGGNMLYRNI LYFPNHLPE.  LRKQTKGVEL QQPEYEPSVH SIDWQVGYAI

clag3.1 VNGFMYAFCF FAISQMYAYF ENINFYITSN FRFLDRYYGV FNKYFINYAI
clag3.2 VNGFMYAFCF FAISQMYAYF ENINFYITSN FRFLDRYYGV FNKYFINYAI
clag2.1 TNGFMYAFCF YSIMPLYAYF ENVNFYIISN FRFLDRYYNA FNKYFINFFK
clag9   SHGLSLSFFT FGMMKAYAYF ENVIFFLRNS IRIFDRFYSI LENYVCMYIK

clag3.1 IKLKEITSDL LIKYEREAYL SMKKYGYLGE VIAARLSPKD KIMNYVHETN
clag3.2 IKLKEITSDL LIKYEREAYL SMKKYGYLGE VIAARLSPKD KIMNYVHETN
clag2.1 TKLKKYTTDV FIKYEYDAYT SMKKYGYLNE VIGSRLSSKN RIVKYIYDSN
clag9   RLFNKLTVDK LLKAMSRAYT STKKEGAYEE AMVSRVRNKE NVVQEVQEDK

clag3.1 EDIMSNLRRY DMENAFKNKM STYVDDFAFF DDCGKNEQFL NERCDYCPVI
clag3.2 EDIMSNLRRY DMENAFKNKM VTYVDDFAFF DDCGKNEQFL NERCDYCPVI
clag2.1 DDIMNNLRRY DMENRFRNKM STYVDEYAFF DDCGKNEVFL NDRCDYCPIV
clag9   GTDITPLPTF DIMDSKQNTN YMYNDNEDYF DDLDDNEQFL NS........
```

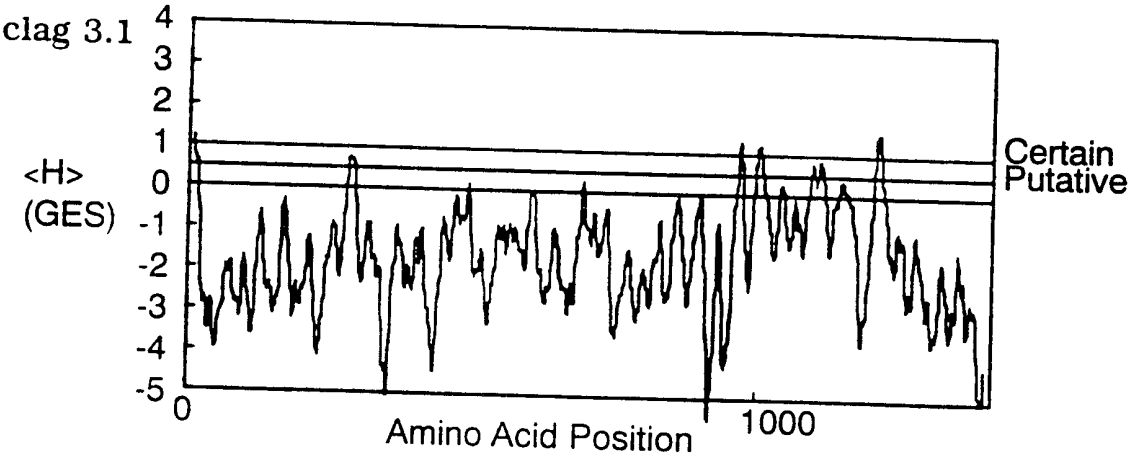
FIGURE 9 (VIII)

```
clag3.1 EEVEETQLFT TTGDKNTNKT TEIKKQTSTY IDTEKMNEAD SADSD.....
clag3.2 EEVEETQLFT TTGDKNTNET TEIKKQTSTY IDTEKMNEAD SADSD.....
clag2.1 EDLCEPDTKE YQP..HTSNI QKVTDKNTTY INYEKLHEES YSQETQSDNT
clag9     ....KDLLYY DDGIDRTKRY ELIPLQRYRY DPF.....  ..........

clag3.1 .DEKDSDTPD DELMISRFH
clag3.2 .DEKDFDTPD NELMIARFH
clag2.1 DDEKDNDLPD TELMITRLQ
clag9   ..........  .........
```

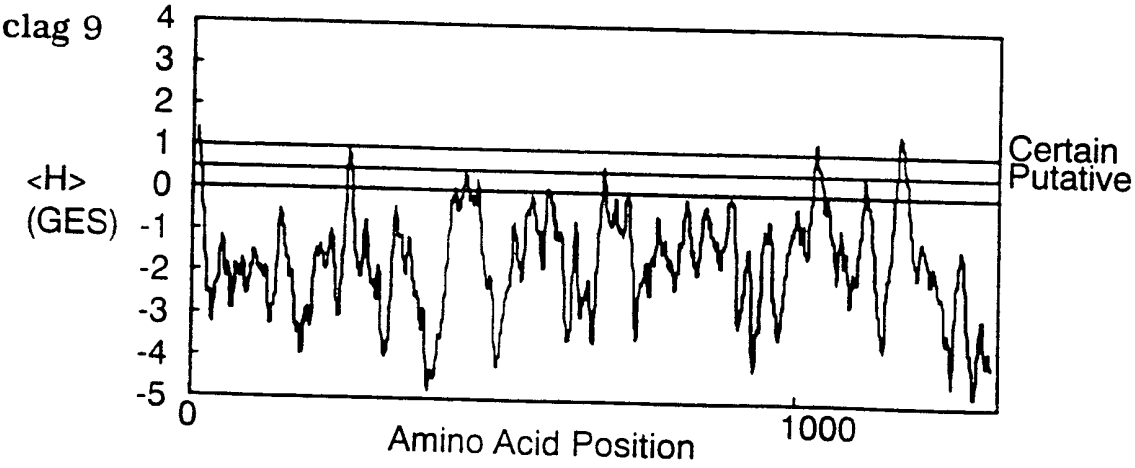
a) clag 2



b) clag 3.1



c) clag 9



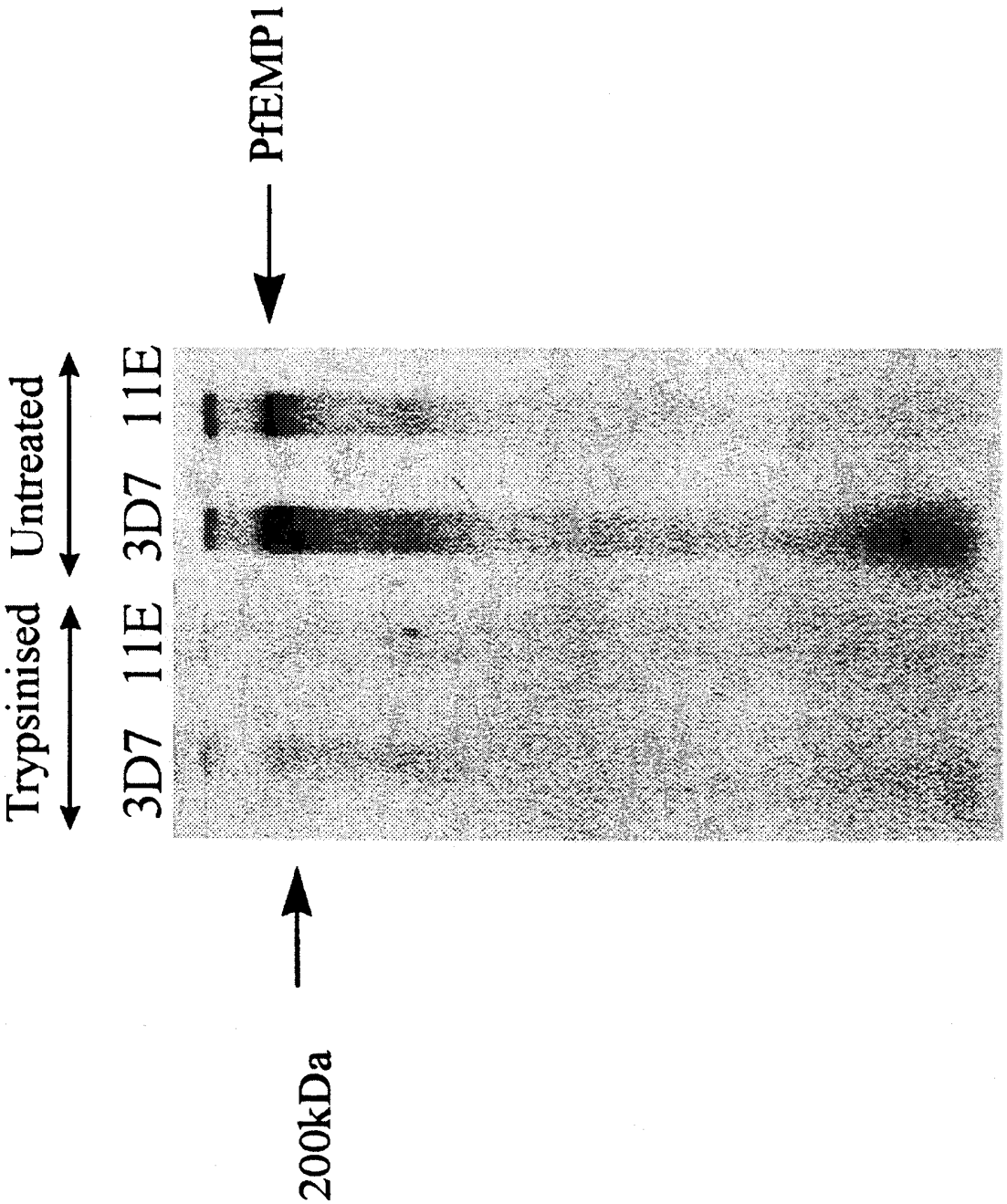


Figure 18

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Gly Lys Leu Gln Tyr Thr Glu Ser Asp Asp Glu Gly Ser Asp Glu Tyr
35 40 45

Cys Glu Gly Gly Tyr His Pro Val Lys Ile Asn Glu Ile Tyr Asn Asp
50 55 60

Arg Tyr Arg Ile Glu Gly Lys Leu Gly Trp Gly His Phe Ser Thr Val
65 70 75 80

Trp Val Ala Thr Asp Leu Lys Ser Lys Pro Leu Lys Phe Val Ala Ile
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Lys Ile Gln Lys Gly Ser Glu Thr Tyr Thr Glu Ser Ala Lys Cys Glu
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Ile Asn Tyr Leu Asn Thr Val Lys Val Asn Ser Phe Asp Ser Ser Trp
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Val Glu Leu Lys Glu Gln Gln Arg Glu Arg Leu Phe His Tyr Asn Met

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Thr Lys Gly Val Val Ser Phe Ile Asp Ser Phe Glu His Lys Gly Pro
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Asn Gly Thr His Ile Cys Met Val Phe Glu Phe Met Gly Pro Asn Leu
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Val Arg Lys Ile Ala Thr His Val Leu Ile Gly Met Gln Tyr Leu His
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Val Ser Pro Leu Thr Thr Ile Pro Lys Pro Lys Asp Tyr Thr Lys Asp
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Thr Asn Leu Ser Glu Lys Lys Lys Val Ile Asn Asp Thr Gln Lys Asn
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Asp Lys Asn Ile Glu Tyr Asp Gln Lys Cys Thr Ser Ser Lys Glu Asn

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Leu His Glu Leu Tyr Met Lys Asn Lys Lys Asn Ile Asp Ser Asn Asn
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Thr Met Asn Asp Leu Gly Asn Asn Gln Asn Ser His Lys Val Val Tyr
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Ile Asn Thr Glu Asp Gly Glu Tyr Cys Ile Arg Pro Tyr Asp Pro Ser
675 680 685

Val Tyr Tyr His Glu Lys Ser Cys Tyr Lys Ile Cys Asp Leu Gly Asn
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Tyr Arg Ala Pro Glu Val Ile Leu Lys Ser Gly Phe Asn Glu Thr Ala
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Gly His Asn Ser Ser Lys Asn Lys Asn Ser Ser Asn Lys Lys Lys Ile
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Asp Val Asn Tyr Lys Ile Gly Asn Asn Gly Asn Asn Ala Tyr Asn Asp
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945 950 955 960

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Phe Asp Ile Asn Tyr Leu Gln His Arg Asn Asp Asn Asn Ser Asn Lys
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Lys Ala Tyr Asn Glu Ser Ile Gln Tyr Glu Met His Asp Phe Gln Gln
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Arg Gln Ile Ser Ala Phe Asn Leu Tyr Leu Asn Tyr Tyr Tyr Phe Met
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Lys Arg Tyr Ser Ser Tyr Gly Thr Lys Lys Thr Leu Tyr Val His Leu
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Leu Asn Leu Thr Gly Leu Leu Ser Asn Asn Lys Lys Asn Tyr Gln Lys
1845 1850 1855

Lys Lys Lys Ile Arg Thr Tyr Leu Ile Phe Cys Leu Tyr Thr Thr Phe
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His Ile Phe Asn Ile Tyr His Asn Tyr Tyr Tyr Tyr Phe Phe Phe Phe
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Phe Leu Leu Ile Leu Val Lys Phe Asp Glu Val Pro Ser Met Leu Gln

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Lys Phe Tyr Val Tyr Leu Thr Lys Gly Leu Lys Ile Gln Lys Val Ser
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Ser Phe Lys Gly Asn Thr Tyr Thr His Ile Tyr Met Gln Lys Tyr Ile
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2005 2010 2015

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Ile Glu Arg Tyr Lys Ile Lys His Asn Tyr Gln Asn Ile Tyr Phe Tyr

2850 2855 2860

Lys Arg Lys Lys Glu Lys Asn Met Lys Tyr Leu Phe Phe Ser Leu Phe
2865 2870 2875 2880

Leu Cys Tyr Asn Leu Ile Val Tyr Ile Tyr Cys Val Ser Lys Asn Ala
2885 2890 2895

Tyr Asn Ile Lys Glu Lys Arg Arg Gly Glu Cys Asn Phe Pro Ile Asn
2900 2905 2910

Asn Gln Arg Cys Asn Asn Asn Met Asn Ser Leu Ile Met Asn Lys Tyr
2915 2920 2925

Leu Tyr Lys Lys Arg Lys His Ser Asn Thr Leu Pro Phe Ile Lys Thr
2930 2935 2940

Tyr Asn Asn Phe Lys Glu Lys Asn Lys Asn Asp Val Val Gln Ile Ser
2945 2950 2955 2960

Tyr Tyr Ser Ile Asn His Asn Lys Lys Tyr Asn Asn Lys Ile His Thr
2965 2970 2975

His Ile Leu Phe Met Asn Asn Asn Asn Asn Asn Asn Asn Asn Ser Asn
2980 2985 2990

Ser Asn Lys Glu Tyr Ile Lys Ala Asn Asn Ala Asn Met Leu Phe Ser
2995 3000 3005

Ile Tyr Asn Lys Ile Ser Glu Asp Gly Lys Thr Lys Asn Ser Leu Leu

3010 3015 3020

Ser Asp Ile Ser Lys Leu Phe Lys Ile Val Lys Glu Ser Lys Leu Ile
3025 3030 3035 3040

Phe Val Thr Gly Phe Leu Leu Thr Thr Leu Ser Ala Ile Val Asp Ser
3045 3050 3055

Tyr Ile Pro Ile Phe Leu Ser Lys Thr Val Ser Phe Val Met Glu Arg
3060 3065 3070

Lys Lys Phe Thr Phe Leu Lys Ile His Lys Thr Asn Leu Ser Val Val
3075 3080 3085

Lys Asn Leu Ile Glu Tyr Leu Lys Phe Tyr Ser Thr Asn Pro Phe His
3090 3095 3100

Met Tyr Val Leu Ile Ser Val Ile Ser Leu Leu Phe Ser Ser Phe Arg
3105 3110 3115 3120

Ser Tyr Ile Phe Asn Val Cys Ala Tyr Val Ser Thr Asn Lys Leu Gln
3125 3130 3135

Lys Tyr Leu Phe Asn Val Leu Leu His Lys Asn Ile Asn Tyr Phe Lys
3140 3145 3150

Lys Lys Gly Lys Gly Glu Leu Ile Ser Arg Leu Asn Ile Asp Ser Ser
3155 3160 3165

Glu Leu Ile Asp Ile Phe Thr Thr Asn Ile Ile Val Leu Phe Arg Asn

3170 3175 3180

Met Ile Lys Met Ala Leu Ser Phe Tyr Phe Leu Tyr Lys Ile Asn Val
3185 3190 3195 3200

His Leu Phe Ile Val Ser Leu Phe Ile Val Phe Ile Ile Ser Asn Ile
3205 3210 3215

Ser Ile Phe Phe Ser Asn Ile Phe Arg Lys Leu Ala Lys Glu Glu Ser
3220 3225 3230

Asn Val Val Ala Gln Ser Asn Asn Ile Val Glu Glu Ser Ile Tyr Asn
3235 3240 3245

Phe Ser Leu Ile Ser Thr Phe Asn Thr His Asn Lys Glu Ile Lys Lys
3250 3255 3260

Tyr Asn Asn Ser Leu Asp Thr Ile Tyr Met Ser Arg Met Lys Leu Gly
3265 3270 3275 3280

Leu Leu Tyr Ile Ile Glu Lys Phe Phe Ile Arg Leu Ile Asp Met Met
3285 3290 3295

Thr Phe Ile Leu Thr Leu Ile Leu Ser Lys Lys Thr Leu Met Tyr Asn
3300 3305 3310

Leu Asn Thr Asp Thr Arg Thr Ile Ile Ser Ser Val Ile Tyr Met Gln
3315 3320 3325

Asn Ile Ile Ala Gln Ser Cys Ile Ile Glu Gln Gln Tyr Ser Arg Val

3330 3335 3340

Gln Glu Leu Ile Gly Asn Ala Glu Glu Val Ile Lys Leu Ile Glu Lys
3345 3350 3355 3360

Asp Asn Met Arg Asn Asn Asn Asn Asn Asn Asn Asn Asp Asn Ile Lys
3365 3370 3375

Leu Val Ser Asn Lys Tyr Asn Phe Phe Ser Ile Leu Phe Asn Ile Asn
3380 3385 3390

Asp Met Lys Asn Phe Ile Phe Asn His Ser Leu Leu Lys Lys Phe Gln
3395 3400 3405

Thr Ile Gln Asn Asn Ser Asp Tyr Val Phe Asn Ile Ile Lys Pro Asn
3410 3415 3420

Tyr Leu Lys Leu Phe Glu Arg Asn Tyr Asn Asn Leu Ile Lys Leu Phe
3425 3430 3435 3440

Phe Asn Glu Lys Asn Phe Asn Gln Cys Asp Glu Ser Leu Phe Lys Asn
3445 3450 3455

Gly Ser Ile Asp Asp Ile Asn Asn Ile Asp Met Tyr Glu Lys Lys Glu
3460 3465 3470

Glu Thr Asn Lys Ile Asn Asp Tyr His Asn Phe Ile Ser Asn Lys Gln
3475 3480 3485

Met Tyr Asp Asn Lys Thr Lys Asp Cys Thr Leu Lys Lys Lys Lys Gln

3490 3495 3500

Asp Asn Ser Phe Tyr Tyr Asn Thr Pro Asn Asn Asn Val Glu Met Lys
3505 3510 3515 3520

Asn Gln Leu Asp Gln His Ser Phe Ser Lys Ser Glu Asn Phe Gln Asn
3525 3530 3535

Lys Leu Lys Lys Lys Ile Gln Glu Ile Asn Met Gln Glu Val Tyr Gln
3540 3545 3550

Phe Ile Lys Asn Asp His Ala Leu Ile Ile Lys Tyr Lys Leu Asp Arg
3555 3560 3565

Lys Phe Ile Arg Phe Leu Lys Thr Asn Tyr Lys Lys Asn Ile Ile Leu
3570 3575 3580

Leu Ile Leu Lys Leu Tyr Lys Glu Arg Asn Asn Ser Val Ser Asp Asn
3585 3590 3595 3600

Phe Leu Phe Leu Phe Asp Asn Ile Ser Ser Phe Lys Asn Leu Ser Ile
3605 3610 3615

Lys Asp Lys Lys Ser Ile Leu Lys Met Ser Asn Ile Thr Asn Lys Thr
3620 3625 3630

Ile Tyr Ile Ile Leu Leu Thr Phe Leu Phe Tyr Asn Tyr Ser Lys Phe
3635 3640 3645

Tyr Tyr Lys Lys Gln Lys Lys Lys Asn Phe Ile Asn Phe Ile Glu Lys

3650 3655 3660

Lys Asn Lys Met Leu Lys Asn Asn Gln Asn Val Glu Arg Gly Gln His
3665 3670 3675 3680

Gly Ser Ser Thr Tyr Glu Lys Met Tyr Glu Ser Met Asp Asp Glu Ile
3685 3690 3695

Asn Ile Asn Asp Val Leu Ser Asp Ala Ile Ser Asp Thr Ile Cys Asp
3700 3705 3710

Asn Ser Asn Asp Thr Ile Arg Asp Asn Ser Asn Asp Thr Ile Cys Asp
3715 3720 3725

Asn Ser Asn Asn Thr Ile Cys Asp Asn Ser Asn Asp Thr Ile Cys Asp
3730 3735 3740

Lys Ser Asn Val Ile Ser Ser Asn Tyr Gln Ser Asn Gln His Leu Tyr
3745 3750 3755 3760

Pro Gln Ile Met Ser Thr Thr Pro Asn Lys Asn Asp Gln Tyr Asn Asn
3765 3770 3775

Pro Thr Asp Asn Leu Glu Leu Asn Asn Glu Ser Val Ile Leu Asn Lys
3780 3785 3790

Thr Lys Ser Arg Thr Lys Lys Lys Arg Asn Leu Tyr Asn Ile Leu Pro
3795 3800 3805

Tyr Ile Val Glu Asn Ala Ile Lys Glu Leu Glu Ile Leu Lys Phe Ile

3810 3815 3820

Asp Ala Asn Tyr Lys Ser Ile Asn Glu Asn Leu Ile Leu Asp Asn Ile
3825 3830 3835 3840

Lys Asp Asn Gln Lys Gly Ser Thr Leu Ile Phe Glu Asn Val Asp Phe
3845 3850 3855

Tyr Phe Ala Lys Tyr Pro Lys Asn Lys Ile Leu Ser Asn Ile Asn Leu
3860 3865 3870

Asn Phe Ser Asn Lys Tyr Thr Tyr Gly Ile Leu Cys Tyr Asn Asp Ser
3875 3880 3885

Gly Lys Asn Tyr Leu Ala Lys Leu Ala Ala Arg Leu Tyr Asn Lys Thr
3890 3895 3900

Tyr Gly Asn Ile Leu Leu Asp Asp Glu Asn Ile Glu Asn Ile Ser Lys
3905 3910 3915 3920

Tyr Ile Leu Thr Lys Lys Ile Ser Leu Val Glu Glu Gln Ser Tyr Ile
3925 3930 3935

Phe Ser Asp Ser Ile Ile Tyr Asn Met Leu Tyr Ser Tyr Asn Cys Ile
3940 3945 3950

Thr Lys Gly Asn Lys Asn Phe Tyr Tyr Leu Asn Tyr Asn Phe Lys Leu
3955 3960 3965

Asn Lys Asn Asn Ile Asn Asn Cys Val His Leu Phe Ser His Asp Asn

3970 3975 3980

Asp Ile Thr Thr Asn Asp Tyr Asn Asn Asn Asn Ile Asn Lys Asn Ile
3985 3990 3995 4000

Asn Ser Asp Asn Tyr Ser Ser Ser Ser Ser Ser Asn Thr Ile Ser Ser
4005 4010 4015

Cys Arg Asn Tyr Glu Gln Tyr Glu Lys Ile Lys Glu Lys Asn Lys Lys
4020 4025 4030

Pro Lys Ile Lys Tyr Lys Ile Lys Glu Asn Lys Pro Ser Ile Tyr Asn
4035 4040 4045

Ile His Asn Thr Thr Asn Asn Asn Thr Val Asp Gln Ser Leu Tyr Thr
4050 4055 4060

Phe Lys Asn Phe Lys Lys Lys Cys Leu Met Cys Gly Ser Leu Ile Asp
4065 4070 4075 4080

Thr Lys Leu Leu Glu Glu Gln Lys Lys Ser Pro Asn Tyr Asn Lys Tyr
4085 4090 4095

Lys Val His Phe Ile Lys Lys Leu Tyr Lys Glu Ile Ile Lys Val Ser
4100 4105 4110

Lys Ile Val Cys Leu Tyr Asp Val Ile Asn Ser Tyr Pro Asp Lys Phe
4115 4120 4125

Phe His Asn Ile Asn Asp

4130

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<213> Plasmodium falciparum

<400> 7

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<210> 8

<211> 36

<212> DNA

<213> Plasmodium falciparum

<400> 8

aactcgagtt aaaaaggatc ataacgataa cgttgc 36

<210> 9

<211> 27

<212> DNA

<213> Plasmodium falciparum

<400> 9

gcggccgctc caattgtagt gctaatg 27

<210> 10

<211> 21

<212> DNA

<213> Plasmodium falciparum

<400> 10

cggaacattc ttctgatgtg g 21

<210> 11

<211> 1469

<212> PRT

<213> Plasmodium falciparum

<400> 11

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Ile Leu Ile Ile Phe Leu Tyr Leu Asn Glu Lys Val Ile Cys Ser Ile
20 25 30

Asn Glu Asn Gln Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Asn Glu Asn Asp Thr Ile Ser Gln Asn Val
50 55 60

Asn Gln His Glu Asn Ile Asn Gln Asn Val Asn Asp Asn Asp Xaa Xaa
65 70 75 80

Xaa Asn Ile Glu Gln Leu Lys Ser Met Ile Gly Asn Asp Glu Leu His
85 90 95

Lys Asn Leu Thr Ile Leu Glu Lys Leu Ile Leu Glu Ser Leu Glu Lys

100 105 110

Asp Lys Leu Lys Tyr Pro Leu Leu Lys Gln Gly Thr Glu Gln Leu Ile
115 120 125

Asp Ile Ser Lys Phe Asn Lys Lys Asn Ile Thr Asp Ala Asp Asp Xaa
130 135 140

Xaa Glu Thr Tyr Ile Ile Pro Thr Val Gln Ser Thr Phe His Asp Ile
145 150 155 160

Val Lys Tyr Glu His Leu Ile Lys Glu Gln Ser Ile Glu Ile Tyr Asn
165 170 175

Ser Asp Ile Ser Asp Lys Ile Lys Lys Lys Ile Phe Ile Val Arg Thr
180 185 190

Leu Lys Thr Ile Lys Leu Met Leu Ile Pro Leu Asn Ser Tyr Lys Gln
195 200 205

Asn Asn Asp Leu Lys Ser Ala Leu Glu Glu Leu Asn Asn Val Phe Thr
210 215 220

Asn Lys Glu Ala Gln Glu Glu Ser Xaa Ser Pro Ile Gly Asp His Gly
225 230 235 240

Thr Phe Phe Arg Lys Leu Leu Thr His Val Arg Thr Ile Lys Glu Asn
245 250 255

Glu Asp Ile Glu Asn Lys Gly Glu Thr Leu Ile Leu Gly Asp Asn Lys

260 265 270

Ile Asp Val Met Asn Ser Asn Asp Phe Phe Phe Thr Thr Asn Ser Asn
275 280 285

Val Lys Phe Met Glu Asn Leu Asp Asp Ile Thr Asn Gln Tyr Gly Leu
290 295 300

Gly Leu Ile Asn His Leu Gly Pro His Leu Ile Ala Leu Gly His Phe
305 310 315 320

Thr Val Leu Lys Leu Ala Leu Lys Asn Tyr Lys Asn Tyr Phe Glu Ala
325 330 335

Lys Ser Ile Lys Phe Phe Ser Trp Gln Lys Ile Leu Glu Phe Ser Met
340 345 350

Ser Asp Arg Phe Lys Val Leu Asp Met Met Cys Asp His Glu Ser Val
355 360 365

Tyr Tyr Ser Glu Lys Lys Arg Arg Lys Thr Tyr Leu Lys Val Asp Arg
370 375 380

Ser Asn Thr Ser Met Glu Cys Asn Ile Leu Glu Tyr Leu Leu His Tyr
385 390 395 400

Phe Asn Lys Tyr Gln Leu Glu Ile Ile Lys Thr Thr Gln Asp Thr Asp
405 410 415

Phe Asp Leu His Gly Met Met Glu His Lys Tyr Ile Lys Asp Tyr Phe

420 425 430

Phe Ser Phe Met Cys Asn Asp Pro Lys Glu Cys Ile Ile Tyr His Thr
435 440 445

Asn Gln Phe Lys Lys Glu Ala Asn Glu Glu Asn Thr Phe Pro Glu Gln
450 455 460

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Glu Glu Pro Asn Arg Gln Ile
465 470 475 480

Ser Ala Phe Asn Leu Tyr Leu Asn Tyr Tyr Tyr Phe Met Lys Arg Tyr
485 490 495

Ser Ser Tyr Gly Val Lys Lys Thr Leu Tyr Val His Leu Leu Asn Leu
500 505 510

Thr Gly Leu Leu Asn Tyr Asp Thr Arg Ala Tyr Val Thr Ser Leu Tyr
515 520 525

Leu Pro Gly Tyr Tyr Asn Ala Val Glu Met Ser Phe Thr Glu Glu Lys
530 535 540

Glu Phe Ser Lys Leu Phe Glu Ser Leu Ile Gln Cys Ile Glu Lys Cys
545 550 555 560

His Ser Xaa Xaa Asp Gln Ala Arg Gln Ile Ser Xaa Xaa Lys Asp Ser
565 570 575

Asn Leu Leu Asn Asn Ile Thr Xaa Xaa Xaa Lys Cys Asp Leu Cys Lys

580 585 590

Gly Ala Phe Leu Tyr Ala Asn Met Lys Phe Asp Glu Val Pro Ser Met
595 600 605

Leu Gln Lys Phe Tyr Val Tyr Leu Thr Lys Gly Leu Lys Ile Gln Lys
610 615 620

Val Ser Ser Leu Ile Lys Thr Leu Asp Ile Tyr Gln Asp Tyr Ser Asn
625 630 635 640

Tyr Leu Ser His Asp Ile Asn Trp Tyr Thr Phe Leu Phe Leu Phe Arg
645 650 655

Leu Thr Ser Phe Lys Glu Ile Ala Lys Lys Asn Val Ala Glu Ala Met
660 665 670

Tyr Leu Asn Ile Lys Asp Glu Asp Thr Phe Asn Lys Thr Val Val Thr
675 680 685

Asn Tyr Trp Tyr Pro Ser Pro Ile Lys Lys Tyr Tyr Thr Leu Tyr Val
690 695 700

Arg Lys His Ile Pro Asn Asn Leu Val Asp Glu Leu Glu Lys Leu Met
705 710 715 720

Lys Ser Gly Thr Leu Glu Lys Met Lys Lys Ser Leu Thr Phe Leu Val
725 730 735

His Val Asn Ser Phe Leu Gln Leu Asp Phe Phe His Gln Leu Asn Glu

740 745 750

Pro Pro Leu Gly Leu Pro Arg Ser Tyr Pro Leu Ser Leu Val Leu Glu
755 760 765

His Lys Phe Lys Glu Trp Met Asn Ser Ser Pro Ala Gly Phe Tyr Phe
770 775 780

Ser Asn Tyr Gln Asn Pro Tyr Ile Arg Lys Asp Leu His Asp Lys Val
785 790 795 800

Leu Ser Gln Lys Phe Glu Pro Pro Lys Met Asn Gln Trp Asn Lys Val
805 810 815

Leu Lys Ser Leu Ile Glu Cys Ala Tyr Asp Met Tyr Phe Glu Gln Arg
820 825 830

His Val Lys Asn Leu Tyr Lys Tyr His Asn Ile Tyr Asn Ile Asn Asn
835 840 845

Lys Leu Met Leu Met Arg Asp Ser Ile Asp Leu Tyr Lys Asn Asn Phe
850 855 860

Asp Asp Val Leu Phe Phe Ala Asp Ile Phe Asn Met Arg Lys Tyr Met
865 870 875 880

Thr Ala Thr Pro Val Tyr Lys Lys Val Lys Asp Arg Val Tyr His Thr
885 890 895

Leu His Ser Ile Thr Gly Asn Ser Val Asn Phe Tyr Lys Tyr Gly Ile

900 905 910

Ile Tyr Gly Phe Lys Val Asn Lys Glu Ile Leu Lys Glu Val Val Asp
915 920 925

Glu Leu Tyr Ser Ile Tyr Asn Phe Asn Thr Asp Ile Phe Thr Asp Thr
930 935 940

Ser Phe Leu Gln Thr Val Tyr Leu Leu Phe Arg Arg Ile Glu Glu Thr
945 950 955 960

Tyr Arg Thr Gln Arg Arg Asp Asp Lys Ile Ser Val Asn Asn Val Phe
965 970 975

Phe Met Asn Val Ala Asn Asn Tyr Ser Lys Leu Asn Lys Glu Glu Arg
980 985 990

Glu Ile Glu Ile His Asn Ser Met Ala Ser Arg Tyr Tyr Ala Lys Thr
995 1000 1005

Met Phe Ala Ala Phe Gln Met Leu Phe Ser Thr Met Leu Ser Asn Asn
1010 1015 1020

Val Asp Asn Leu Asp Lys Ala Tyr Gly Leu Ser Glu Asn Ile Gln Val
1025 1030 1035 1040

Ala Thr Ser Thr Ser Ala Phe Leu Thr Phe Ala Tyr Val Tyr Asn Gly
1045 1050 1055

Ser Ile Met Asp Ser Val Thr Asn Ser Leu Leu Pro Pro Tyr Ala Lys

1060 1065 1070

Lys Pro Ile Thr Gln Leu Lys Tyr Gly Lys Thr Phe Val Phe Ser Asn
1075 1080 1085

Tyr Phe Met Leu Ala Ser Lys Met Tyr Asp Met Leu Asn Tyr Lys Asn
1090 1095 1100

Leu Ser Leu Leu Cys Glu Tyr Gln Ala Val Ala Ser Ala Asn Phe Tyr
1105 1110 1115 1120

Ser Ala Lys Lys Val Gly Gln Phe Leu Gly Arg Lys Phe Leu Pro Ile
1125 1130 1135

Thr Thr Tyr Phe Leu Val Met Arg Ile Ser Trp Thr His Ala Phe Thr
1140 1145 1150

Thr Gly Gln His Leu Ile Ser Ala Phe Gly Ser Pro Ser Ser Thr Ala
1155 1160 1165

Asn Gly Lys Ser Asn Ala Ser Gly Tyr Lys Ser Pro Glu Ser Phe Phe
1170 1175 1180

Phe Thr His Gly Leu Ala Ala Glu Ala Ser Lys Tyr Leu Phe Phe Tyr
1185 1190 1195 1200

Phe Phe Thr Asn Leu Tyr Leu Asp Ala Tyr Lys Ser Phe Pro Gly Gly
1205 1210 1215

Phe Gly Pro Ala Ile Lys Glu Gln Thr Gln His Val Gln Glu Gln Thr

1220 1225 1230

Tyr Glu Arg Lys Pro Ser Val His Ser Phe Asn Arg Asn Phe Phe Met
1235 1240 1245

Glu Leu Val Asn Gly Phe Met Tyr Ala Phe Cys Phe Phe Ala Ile Ser
1250 1255 1260

Gln Met Tyr Ala Tyr Phe Glu Asn Ile Asn Phe Tyr Ile Thr Ser Asn
1265 1270 1275 1280

Phe Arg Phe Leu Asp Arg Tyr Tyr Gly Val Phe Asn Lys Tyr Phe Ile
1285 1290 1295

Asn Tyr Ala Ile Ile Lys Leu Lys Glu Ile Thr Ser Asp Leu Leu Ile
1300 1305 1310

Lys Tyr Glu Arg Glu Ala Tyr Leu Ser Met Lys Lys Tyr Gly Tyr Leu
1315 1320 1325

Gly Glu Val Ile Ala Ala Arg Leu Ser Pro Lys Asp Lys Ile Met Asn
1330 1335 1340

Tyr Val His Glu Thr Asn Glu Asp Ile Met Ser Asn Leu Arg Arg Tyr
1345 1350 1355 1360

Asp Met Glu Asn Ala Phe Lys Asn Lys Met Ser Thr Tyr Val Asp Asp
1365 1370 1375

Phe Ala Phe Phe Asp Asp Cys Gly Lys Asn Glu Gln Phe Leu Asn Glu

1380 1385 1390

Arg Cys Asp Tyr Cys Pro Val Ile Glu Glu Val Glu Glu Thr Gln Leu
1395 1400 1405

Phe Thr Thr Thr Gly Asp Lys Asn Thr Asn Lys Thr Thr Glu Ile Lys
1410 1415 1420

Lys Gln Thr Ser Thr Tyr Ile Asp Thr Glu Lys Met Asn Glu Ala Asp
1425 1430 1435 1440

Ser Ala Asp Ser Asp Xaa Xaa Xaa Xaa Xaa Xaa Asp Glu Lys Asp Ser
1445 1450 1455

Asp Thr Pro Asp Asp Glu Leu Met Ile Ser Arg Phe His
1460 1465

<210> 12

<211> 1469

<212> PRT

<213> Plasmodium falciparum

<400> 12

Xaa Xaa Xaa Xaa Xaa Xaa Met Val Ser Phe Phe Lys Thr Pro Ile Ile
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Ile Phe Phe Phe Leu Leu Cys Leu Asn Glu Lys Val Leu Cys Ser Ile
20 25 30

Asn Glu Asn Glu Asn Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Gly Glu Asn Lys Asn Glu Asn Ala Asn Val
50 55 60

Asn Thr Pro Glu Asn Leu Asn Lys Leu Leu Asn Glu Tyr Asp Xaa Xaa
65 70 75 80

Xaa Asn Ile Glu Gln Leu Lys Ser Met Ile Gly Asn Asp Glu Leu His
85 90 95

Lys Asn Leu Thr Ile Leu Glu Lys Leu Ile Leu Glu Ser Leu Glu Lys
100 105 110

Asp Lys Leu Lys Tyr Pro Leu Leu Lys Gln Gly Thr Glu Gln Leu Ile
115 120 125

Asp Ile Ser Lys Phe Asn Lys Lys Asn Ile Thr Asp Ala Asp Asp Xaa
130 135 140

Xaa Glu Thr Tyr Ile Ile Pro Thr Val Gln Ser Ser Phe His Asp Ile
145 150 155 160

Val Lys Tyr Glu His Leu Ile Lys Glu Gln Ser Ile Glu Ile Tyr Asn
165 170 175

Ser Asp Ile Ser Asp Lys Ile Lys Lys Lys Ile Phe Ile Val Arg Thr
180 185 190

Leu Lys Thr Ile Lys Leu Met Leu Ile Pro Leu Asn Ser Tyr Lys Gln
195 200 205

Asn Asn Asp Leu Lys Ser Ala Leu Glu Glu Leu Asn Asn Val Phe Thr
210 215 220

Asn Lys Glu Ala Gln Lys Glu Ser Xaa Ser Pro Ile Gly Asp His Gly
225 230 235 240

Thr Phe Phe Arg Lys Leu Leu Thr His Val Arg Thr Ile Lys Glu Asn
245 250 255

Glu Asp Ile Glu Asn Lys Gly Glu Thr Leu Ile Leu Gly Asp Asn Lys
260 265 270

Ile Asp Val Met Asn Ser Asn Asp Phe Phe Phe Thr Thr Asn Ser Asn
275 280 285

Val Lys Phe Met Glu Asn Leu Asp Asp Ile Thr Asn Gln Tyr Gly Leu
290 295 300

Gly Leu Ile Asn His Leu Gly Pro His Leu Ile Ala Leu Gly His Phe
305 310 315 320

Val Val Leu Lys Leu Ala Leu Lys Asn Tyr Lys Asn Tyr Phe Glu Ala
325 330 335

Lys Asn Ile Lys Phe Phe Ser Trp Gln Lys Ile Leu Glu Phe Ser Met
340 345 350

Ser Asp Arg Phe Lys Val Leu Asp Met Met Cys Asn His Glu Ser Val
355 360 365

Tyr Tyr Ser Glu Lys Lys Arg Arg Lys Thr Tyr Leu Lys Val Asp Arg
370 375 380

Ser Ser Thr Ser Met Glu Cys Asn Ile Leu Glu Tyr Leu Leu His Tyr
385 390 395 400

Phe Asn Lys Tyr Gln Leu Glu Ile Ile Lys Thr Thr Gln Asp Thr Asp
405 410 415

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

Phe Ser Phe Met Cys Asn Asp Pro Lys Glu Cys Ile Ile Tyr His Thr
435 440 445

Asn Gln Phe Lys Lys Glu Ala Asn Glu Glu Asn Thr Phe Pro Glu Gln
450 455 460

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Glu Glu Pro Asn Arg Gln Ile
465 470 475 480

Ser Ala Phe Asn Leu Tyr Leu Asn Tyr Tyr Tyr Phe Met Lys Arg Tyr
485 490 495

Ser Ser Tyr Gly Thr Lys Lys Thr Leu Tyr Val His Leu Leu Asn Leu
500 505 510

Thr Gly Leu Leu Asn His Asp Thr Arg Ala Tyr Val Thr Ser Leu Tyr
515 520 525

Leu Pro Gly Tyr Tyr Asn Ala Val Glu Met Ser Phe Thr Asp Asp Lys
530 535 540

Glu Phe Ser Thr Leu Phe Glu Ser Leu Ile Gln Cys Ile Glu Lys Cys
545 550 555 560

His Ser Xaa Xaa Asp Gln Ala Arg Gln Ile Ser Xaa Xaa Lys Asp Ser
565 570 575

Asn Leu Leu Asn Asn Ile Thr Xaa Xaa Xaa Lys Cys Asp Leu Cys Lys
580 585 590

Gly Ala Phe Leu Tyr Ala Asn Xaa Xaa Xaa Xaa Xaa Ile Pro Ser Met
595 600 605

Leu Gln Lys Phe Tyr Val Tyr Leu Thr Lys Gly Leu Lys Ile Gln Lys
610 615 620

Val Ser Ser Leu Ile Lys Thr Leu Asp Ile Tyr Gln Asp Tyr Ser Asn
625 630 635 640

Phe Leu Ser His Asp Ile Asn Trp Tyr Thr Phe Leu Phe Leu Phe Arg
645 650 655

Leu Thr Ser Phe Lys Glu Ile Ala Asn Lys Asn Val Ala Glu Ala Met
660 665 670

Tyr Leu Asn Ile Lys Asp Glu Asp Thr Phe Asn Lys Thr Ile Val Thr
675 680 685

Asn Tyr Trp Tyr Pro Ser Pro Ile Lys Lys Tyr Tyr Thr Leu Tyr Val
690 695 700

Arg Lys His Ile Pro Asn Asn Leu Val Asp Glu Leu Glu Lys Leu Met
705 710 715 720

Lys Ser Gly Thr Leu Glu Lys Met Lys Lys Ser Leu Thr Phe Leu Val
725 730 735

His Val Asn Ser Phe Leu Gln Leu Asp Phe Phe His Gln Leu Asn Glu
740 745 750

Pro Pro Leu Gly Leu Pro Arg Ser Tyr Pro Leu Ser Leu Val Leu Glu
755 760 765

His Lys Phe Lys Glu Trp Met Asp Ser Ser Pro Ala Gly Phe Tyr Phe
770 775 780

Ser Asn Tyr Gln Asn Pro Tyr Ile Arg Lys Asp Leu His Asp Lys Val
785 790 795 800

Leu Ser Gln Lys Phe Glu Pro Pro Lys Met Asn Gln Trp Asn Lys Val
805 810 815

Leu Lys Ser Leu Ile Glu Cys Ala Tyr Asp Met Tyr Phe Glu Gln Arg
820 825 830

His Val Lys Asn Leu Tyr Lys Tyr His Asn Ile Tyr Asn Ile Asn Asn
835 840 845

Lys Leu Met Leu Met Arg Asp Ser Ile Asp Leu Tyr Lys Asn Asn Phe
850 855 860

Asp Asp Val Leu Phe Phe Ala Asp Ile Phe Asn Met Arg Lys Tyr Met
865 870 875 880

Thr Ala Thr Pro Val Tyr Lys Lys Val Lys Asp Arg Val Tyr His Thr
885 890 895

Leu His Ser Ile Thr Gly Asn Ser Val Asn Phe Tyr Lys Tyr Gly Ile
900 905 910

Ile Tyr Gly Phe Lys Val Asn Lys Glu Ile Leu Lys Glu Val Val Asp
915 920 925

Glu Leu Tyr Ser Ile Tyr Asn Phe Asn Thr Asp Ile Phe Thr Asp Thr
930 935 940

Ser Phe Leu Gln Thr Val Tyr Leu Leu Phe Arg Arg Ile Glu Glu Thr
945 950 955 960

Tyr Arg Thr Gln Arg Arg Asp Asp Lys Ile Ser Val Asn Asn Val Phe
965 970 975

Phe Met Asn Val Ala Asn Asn Tyr Ser Lys Leu Asn Lys Glu Glu Arg
980 985 990

Glu Ile Glu Ile His Asn Ser Met Ala Ser Arg Tyr Tyr Ala Lys Thr
995 1000 1005

Met Phe Ala Ala Phe Gln Met Leu Phe Ser Thr Met Leu Ser Asn Asn
1010 1015 1020

Val Asp Asn Leu Asp Lys Ala Tyr Gly Leu Ser Glu Asn Ile Gln Val
1025 1030 1035 1040

Ala Thr Ser Thr Ser Ala Phe Leu Thr Phe Ala Tyr Val Tyr Asn Gly
1045 1050 1055

Ser Ile Met Asp Ser Val Thr Asn Ser Leu Leu Pro Pro Tyr Ala Lys
1060 1065 1070

Lys Pro Ile Thr Gln Leu Lys Tyr Gly Lys Thr Phe Val Phe Ser Asn
1075 1080 1085

Tyr Phe Met Leu Ala Ser Lys Met Tyr Asp Met Leu Asn Tyr Lys Asn
1090 1095 1100

Leu Ser Leu Leu Cys Glu Tyr Gln Ala Val Ala Ser Ala Asn Phe Tyr
1105 1110 1115 1120

Ser Ala Lys Lys Val Gly Gln Phe Leu Gly Arg Lys Phe Leu Pro Ile
1125 1130 1135

Thr Thr Tyr Phe Leu Val Met Arg Ile Ser Trp Thr His Ala Phe Thr
1140 1145 1150

Thr Gly Gln His Leu Ile Cys Ala Phe Asp Xaa Pro Lys Arg Cys Thr
1155 1160 1165

Pro Asp Cys Lys Asn Ser Thr Ser Tyr Lys Ser Pro Gln Xaa Xaa Ser
1170 1175 1180

Phe Phe Tyr Gly Trp Pro Pro Ser Ser Glu Thr Tyr Leu Phe Phe Tyr
1185 1190 1195 1200

Phe Phe Thr Asn Leu Tyr Leu Asp Ala Tyr Lys Ser Phe Pro Gly Gly
1205 1210 1215

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Gln Met Tyr Ala Tyr Phe Glu Asn Ile Asn Phe Tyr Ile Thr Ser Asn
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1330 1335 1340

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1345 1350 1355 1360

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1365 1370 1375

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1395 1400 1405

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His Arg Thr Tyr Glu Thr Leu Lys Lys Ser Pro Ile Glu Asn Pro Gly
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Gly Leu Ile Asn Asp Leu Gly Pro His Leu Ile Ala Leu Gly His Phe
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Met Val Leu Lys Leu Ala Leu Lys Asn Tyr Lys Asn Tyr Phe Glu Ala
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Ser Gly Ser Ser Met Glu Cys Asn Ile Leu Glu Phe Leu Ile His Tyr
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Phe Glu Leu His Gly Met Met Glu His Lys Asn Ile Lys Asp Tyr Phe
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Asn Ser Ser His Asn Tyr Phe Xaa Xaa Xaa Leu His Glu Ile Thr Lys
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Cys Asp Leu Leu Lys Phe Glu Xaa Xaa Xaa Xaa Glu Val Pro Ser Met
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755 760 765

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995 1000 1005

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00213

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C12N 15/30, A61K 38/16 C07K 14/445 C12Q 1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N 15/30

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See extra sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMBL AL010142 (4 December 1997) THE SANGER CENTRE Whole sequence	1-5, 10 11-15, 20, 21
X	EMBL AL010163 (4 December 1997) THE SANGER CENTRE Whole sequence	1-5, 10 11-15, 20, 21
X	EMBL X03240, J01400, J01402, J01403, J01406, J01408, U01521, A00563 (2 July 1986) Each sequence	1-5, 10, 11-15, 20, 21

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1999	-4 MAY 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **ALISTAIR BESTOW** Telephone No.: (02) 6283 2414

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00213

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 97/19168 (UNITED STATES ARMY MEDICAL RESEARCH MATERIAL COMMAND) 29 May 1997	
X	Whole document	1-4, 10, 11-14, 20, 21
	"Molecular basis for evasion of host immunity and pathogenesis in malaria", R. RAMASAMY, *Biochimica et Biophysica Acta,* 1406(1), 27 February 1998, pp 10-27	
X	Page 13	1-4, 10, 11-14, 20, 21
	"Identification of *Plasmodium falciparum* Erythrocyte Membrane Protein 1 (PFEMP1) as the Rosetting Ligand of the Malaria Parasite *P. falciparum*", Q. CHEN et al., *J. Exp. Med.*, 187(1), 5 January 1998, pp 15-23	
X	Pages 20-22	1-4, 10, 11-14, 20, 21
	"*Plasmodium falciparum* AARPI, a Giant Protein Containing Repeated Motif Rich in Asparagine and Aspartate Residues, is Associated with the Infected Erythrocyte Membrane", J. BURALE et al., *Infection and Immunity*, 65(8), 1997, pages 3003-3010	
X	Pages 3003, 3008, 3009	1-4, 10 11-14, 20, 21
	"Disruption of a novel open reading frame of *Plasmodium falciparum* chromosome 9 by subtelomeric and internal deletions can lead to loss or maintenance of cytoadherance", P. BOURKE et al., *Molecular and Biochemical Parasitology*, 82(1996), pages 25-36	
X	Whole document	1-4, 10 11-14, 20, 21
	"Synthetic pepties based on motifs present in human band 3 protein inhibit cytoadherance/sequestration of the malaria parasite *Plasmodium falciparum*" I Crandal et al, *Proc. Natl. Acad Sci. USA*, 90, May 1993, pages 4703 - 4707	
X	Whole Document	1-4,10 11-14, 20, 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00213

Box B

Electronic Databases:

WPAT: (C12N-015/30/IC or plasmodium or falciparum or malaria#) and (bind# or erythrocyte: or (red blood cell:) or RBC)

Medline: (malaria/CT or plasmodium/CT) and ((cell binding)) or cytoadher? or adher? or (erythrocyte bindng)) and (gene or sequence)

CAS: plasmodium/IT and ((cel binding) or cytoadher? or adhere? or (erythrocyte binding)) and (gene or sequence)

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: B

Electronic Data Bases

WPAT

(C12N-015/30/IC or Plasmodium or falciparum or malaria#) and (Bind# or Erythrocyte: or (Red Blood Cell: or RBC))

MEDLINE

(Malaria/CT or Plasmodium/CT) and (Cell binding) or cytoadher? or Adher? or (Erythrocyte Binding)) and (gene or sequence)

Chemical Abstracts

Plasmodium/CT and ((Cell binding) or cytoadhere? or adher? or (Erythrocyte binding)) and (gene or sequence)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU 99/00213

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
WO	9719168	AU	10500/97	EP	861320

END OF ANNEX