

Applicant

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5 NOVEL MALARIA VACCINES AND ANTIBODIES BINDING TO PLASMODIUM
 SPOROZOITES

10 The present invention relates to the field of malaria medication, in particular to malaria vaccination and to antibodies binding to plasmodium sporozoites, in particular to plasmodium circumsporozoite protein.

15 Malaria is a mosquito-borne infectious disease affecting humans and other animals caused by parasitic protozoans of the genus *Plasmodium*. The genus *Plasmodium* includes about 200 species with five species regularly infecting humans, while other species infect birds, reptiles, rodents and various primates. *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* together account for nearly all human infections with *Plasmodium* species, with *P. falciparum* accounting for the overwhelming majority of malaria deaths. Malaria symptoms typically include fever, feeling tired, vomiting, and headaches. In severe cases it can cause yellow skin, seizures, coma, or death.

20 Malaria is most commonly transmitted by an infected female *Anopheles* mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood. Namely, during a *Plasmodium falciparum* infection, the female Anopheles mosquito injects a small number of sporozoites (~10-100) into the skin, after which they travel to the liver to
25 invade hepatocytes (Crompton et al. (2014) *Annu Rev Immunol* 32, 157-187). In hepatocytes the sporozoites reproduces asexually (tissue schizogony), producing thousands of merozoites. These infect new red blood cells and initiate a series of asexual multiplication cycles (blood schizogony) that produce 8 to 24 new infective merozoites, at which point the cells burst and the infective cycle begins anew. Other merozoites develop into immature gametocytes,
30 which are the precursors of male and female gametes. When a fertilized mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut.

The male and female gametocytes fuse and form an ookinete — a fertilized, motile zygote. Ookinetes develop into new sporozoites that migrate to the insect's salivary glands, ready to infect a new vertebrate host.

- 5 Although sporozoites are not associated with clinical symptoms, this is a time when parasite numbers in the host are low and their eradication can completely abrogate infection. Accordingly, the sporozoite and liver stages of the *P. falciparum* parasite are key targets of current malaria vaccine candidates, as a vaccine that successfully protects against these stages would be able to prevent both malaria infection and transmission. Therefore, subunit vaccines
10 based on circumsporozoite protein (CSP), such as RTS,S, are at the center of the malaria vaccine effort.

- The *Plasmodium* circumsporozoite protein (CSP) is an approximately 42 kD soluble protein that can readily be made using an *E. coli* expression system. CSP is a secreted protein of the
15 sporozoite stage of *Plasmodium*. CSP forms a dense coat on the parasite surface and has been hypothesized to mediate many of the initial interactions between the sporozoite and its two hosts (Ménard R., 2000, *Microbes Infect.* 2:633–642; Sinnis P. and Nardin E., 2002, Sporozoite antigens: biology and immunology of the circumsporozoite protein and thrombospondin related anonymous protein. *In* Malaria Immunology. P. Perlmann and M.
20 Troye-Blomberg, editors. S. Karger AG, Basel, Switzerland. 70–96). The structure and function of CSP is highly conserved across the various strains of malaria that infect humans, non-human primates and rodents. The amino-acid sequence of CSP comprises an immunodominant central repeat region, that is diverse across *Plasmodium* species (NANP-repeat region in case of *P. falciparum*). Flanking the repeats are two conserved motifs at the
25 N- and C- termini, namely region I, a 5-aa sequence at the N terminus of the repeats, and a known cell-adhesive motif C-terminal to the repeats termed the type I thrombospondin repeat (TSR). Those conserved motifs are implicated in protein processing as the parasite travels from the mosquito to the mammalian vector.
- 30 CSP is known to play a crucial role in the migration of the sporozoites from the midgut walls of infected mosquitoes to the mosquito salivary glands. Additionally, CSP is involved in hepatocyte binding in the mammalian host with the N-terminus and central repeat region of

CSP initially facilitate parasite binding. On the hepatocyte surface proteolytic cleavage at region 1 of the N-terminus exposes the adhesive domain of the C-terminus, thereby priming the parasites for invasion of the liver (Coppi et al. (2005) *J Exp Med* 201, 27-33).

5 At present, the leading malaria vaccine is RTS,S/AS01 (trade name Mosquirix), which is a recombinant protein-based malaria vaccine. RTS,S is a hybrid protein particle, formulated in a multi-component adjuvant named AS01. The RTS,S vaccine antigen consists of 19 NANP amino acid repeat units followed by the complete C-terminal domain minus the GPI anchor of the CS antigen, fused to the Hepatitis B virus S protein. The S protein corresponds to the
10 surface antigen of Hepatitis B virus (HBsAg). Approved for use by European regulators in July 2015, it is not only the world's first licensed malaria vaccine, but the first vaccine licensed for use against a parasitic disease of any kind. Even though RTS,S causes the production of antibodies capable of preventing the invasion of hepatocytes and additionally elicits a cellular response enabling the destruction of infected hepatocytes, RTS,S presented problems in trials
15 due to its poor immunogenicity. RTS,S attempted to avoid these by fusing the protein with a surface antigen from hepatitis B, hence creating a more potent and immunogenic vaccine. Moreover, the RTS,S protein had to be formulated in the potent adjuvant AS01, a liposome-based formulation comprising the immunostimulants monophosphoryl lipid A (MPL, a toll-like receptor 4 agonist) and QS-21 (a derivative of Quill A). However, the level of efficacy of
20 RTS,S/AS01 remained behind expectations. In particular, the protective effect of the vaccine is known to decline rapidly after vaccination. The effects of a booster dose were positive, even though overall efficacy seem to wane with time. After four years reductions were 36 percent for children who received three shots and a booster dose. Missing the booster dose reduced the efficacy against severe malaria to a negligible effect. The vaccine was shown to
25 be less effective for infants. Three doses of vaccine plus a booster reduced the risk of clinical episodes by 26 percent over three years, but offered no significant protection against severe malaria.

Moreover, another factor that has complicated the development of such vaccines is the
30 difficulty in identifying robust correlates of protection. Antibodies have been shown to inhibit sporozoite invasion of hepatocytes in *in vitro* functional assays, but their role in the protection of malaria-vaccinated individuals remains unclear.

Accordingly, there is still a need of a more potent malaria vaccine preventing malaria infection and transmission. Moreover, there is still a need of specific antibodies, in particular of antibodies potentially inhibiting sporozoite invasion and liver stage parasite multiplication *in vivo*.

In view of the above, it is the object of the present invention to overcome the drawbacks of current malaria antibodies and vaccines outlined above. In particular, it is the object of the present invention to provide a malaria vaccine, which is superior to the malaria vaccines of the prior art, for example due to its potency. Moreover, it is an object of the present invention to provide antibodies, which are superior to the malaria antibodies of the prior art, for example by potentially inhibiting sporozoite invasion and liver stage parasite multiplication *in vivo*.

This object is achieved by means of the subject-matter set out below and in the appended claims.

Although the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodologies, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

In the following, the elements of the present invention will be described. These elements may be listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and preferred embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description should be understood to support and encompass embodiments which combine the explicitly described embodiments with any number of the disclosed and/or preferred elements. Furthermore, any permutations and combinations of all described elements in this application should be

considered disclosed by the description of the present application unless the context indicates otherwise.

Throughout this specification and the claims which follow, unless the context requires
5 otherwise, the term "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated member, integer or step but not the exclusion of any other non-stated member, integer or step. The term "consist of" is a particular embodiment of the term "comprise", wherein any other non-stated member, integer or step is excluded. In the context of the present invention, the term "comprise" encompasses the term
10 "consist of". The term "comprising" thus encompasses "including" as well as "consisting" *e.g.*, a composition "comprising" X may consist exclusively of X or may include something additional *e.g.*, X + Y.

The terms "a" and "an" and "the" and similar reference used in the context of describing the
15 invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were
20 individually recited herein. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

The word "substantially" does not exclude "completely" *e.g.*, a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word
25 "substantially" may be omitted from the definition of the invention.

The term "about" in relation to a numerical value x means $x \pm 10\%$.

The term "disease" as used herein is intended to be generally synonymous, and is used
30 interchangeably with, the terms "disorder" and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that

impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration and/or quality of life.

As used herein, reference to "treatment" of a subject or patient is intended to include prevention, prophylaxis, attenuation, amelioration and therapy. The terms "subject" or "patient" are used interchangeably herein to mean all mammals including humans. Examples of subjects include humans, cows, dogs, cats, horses, goats, sheep, pigs, and rabbits. Preferably, the subject or patient is a human.

As used herein, the terms "peptide", "polypeptide", and "protein" are used interchangeably. The terms "peptide", "polypeptide", and "protein" and variations of these terms typically refer to a molecule, in particular a peptide, an oligopeptide, a polypeptide or a protein, such as a fusion protein, comprising at least two amino acids joined to each other by a normal peptide bond, or by a modified peptide bond, such as for example in the cases of isosteric peptides. For example, a "classical" peptide, polypeptide or protein is typically composed of amino acids selected from the 20 amino acids defined by the genetic code, linked to each other by a normal peptide bond. A peptide, polypeptide or protein can be composed of L-amino acids and/or D-amino acids. Preferably, a peptide, polypeptide or protein is either (entirely) composed of L-amino acids or (entirely) of D-amino acids. In particular, the terms "peptide", "polypeptide", "protein" also include "peptidomimetics" which are defined as peptide analogs containing non-peptidic structural elements, which peptides are capable of mimicking or antagonizing the biological action(s) of a natural parent peptide. A peptidomimetic lacks classical peptide characteristics such as enzymatically scissile peptide bonds. In particular, a peptide, polypeptide or protein may comprise amino acids other than the 20 amino acids defined by the genetic code in addition to these amino acids, or it can be composed of amino acids other than the 20 amino acids defined by the genetic code. In particular, a peptide, polypeptide or protein in the context of the present invention can equally be composed of amino acids modified by natural processes, such as post-translational maturation processes or by chemical processes, which are well known to a person skilled in the art. Such modifications are fully detailed in the literature. These modifications can appear anywhere in the polypeptide: in the peptide skeleton, in the amino acid chain or even at the carboxy- or amino-terminal ends. In particular, a peptide or polypeptide can be branched

following an ubiquitination or be cyclic with or without branching. This type of modification can be the result of natural or synthetic post-translational processes that are well known to a person skilled in the art. The terms "peptide", "polypeptide", "protein" in the context of the present invention in particular also include modified peptides, polypeptides and proteins. For example, peptide, polypeptide or protein modifications can include acetylation, acylation, ADP-ribosylation, amidation, covalent fixation of a nucleotide or of a nucleotide derivative, covalent fixation of a lipid or of a lipidic derivative, the covalent fixation of a phosphatidylinositol, covalent or non-covalent cross-linking, cyclization, disulfide bond formation, demethylation, glycosylation including pegylation, hydroxylation, iodization, methylation, myristoylation, oxidation, proteolytic processes, phosphorylation, prenylation, racemization, selenoylation, sulfatation, amino acid addition such as arginylation or ubiquitination. Such modifications are fully detailed in the literature (Proteins Structure and Molecular Properties (1993) 2nd Ed., T. E. Creighton, New York ; Post-translational Covalent Modifications of Proteins (1983) B. C. Johnson, Ed., Academic Press, New York ; Seifter et al. (1990) Analysis for protein modifications and nonprotein cofactors, Meth. Enzymol. 182: 626-646 and Rattan et al., (1992) Protein Synthesis: Post-translational Modifications and Aging, Ann NY Acad Sci, 663: 48-62). Accordingly, the terms "peptide", "polypeptide", "protein" preferably include for example lipopeptides, lipoproteins, glycopeptides, glycoproteins and the like.

As used herein a "(poly)peptide" comprises a single chain of amino acid monomers linked by peptide bonds as explained above. A "protein", as used herein, comprises one or more, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 (poly)peptides, i.e. one or more chains of amino acid monomers linked by peptide bonds as explained above. Preferably, a protein according to the present invention comprises 1, 2, 3, or 4 polypeptides.

The term "recombinant protein", as used herein, refers to any protein which is prepared, expressed, created or isolated by recombinant means, and which is in particular not occurring in nature.

As used herein, the term "antibody" encompasses various forms of antibodies including, without being limited to, whole antibodies, antibody fragments, in particular antigen binding

fragments, human antibodies, chimeric antibodies, humanized antibodies, recombinant antibodies and genetically engineered antibodies (variant or mutant antibodies) as long as the characteristic properties according to the invention are retained. Human antibodies and monoclonal antibodies are preferred and especially preferred are human monoclonal antibodies, in particular as recombinant human monoclonal antibodies.

Human antibodies are well-known in the art (van Dijk, M. A., and van de Winkel, J. G., *Curr. Opin. Chem. Biol.* 5 (2001) 368-374). In particular, human antibodies can also be produced in transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire or a selection of human antibodies in the absence of endogenous immunoglobulin production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge (see, e.g., Jakobovits, A., et al., *Proc. Natl. Acad. Sci. USA* 90 (1993) 2551-2555; Jakobovits, A., et al., *Nature* 362 (1993) 255-258; Bruggemann, M., et al., *Year Immunol.* 7 (1993) 3340). Human antibodies can also be produced in phage display libraries (Hoogenboom, H. R., and Winter, G., *J. Mol. Biol.* 227 (1992) 381-388; Marks, J. D., et al., *J. Mol. Biol.* 222 (1991) 581-597). The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); and Boerner, P., et al., *J. Immunol.* 147 (1991) 86-95). Most preferably, human monoclonal antibodies are prepared by using improved EBV-B cell immortalization as described in Traggiai E, Becker S, Subbarao K, Kolesnikova L, Uematsu Y, Gismondo MR, Murphy BR, Rappuoli R, Lanzavecchia A. (2004): An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. *Nat Med.* 10(8):871-5. The term "human antibody" as used herein also comprises such antibodies which are modified, e.g. in the variable region, to generate the properties according to the invention as described herein. As used herein, the term "variable region" (variable region of a light chain (V_L), variable region of a heavy chain (V_H)) denotes each of the pair of light and heavy chains which is involved directly in binding the antibody to the antigen.

Antibodies of the invention can be of any isotype (e.g., IgA, IgG, IgM i.e. an α , γ or μ heavy chain), but will preferably be IgG. Within the IgG isotype, antibodies may be of IgG1, IgG2,

IgG3 or IgG4 subclass, whereby IgG1 is preferred. Antibodies of the invention may have a κ or a λ light chain.

Preferably, the antibody according to the present invention, or the antigen binding fragment thereof, is a purified antibody, a single chain antibody, Fab, Fab', F(ab')₂, Fv or scFv.

The antibodies of the invention may thus preferably be human antibodies, monoclonal antibodies, human monoclonal antibodies, recombinant antibodies or purified antibodies. The invention also provides fragments of the antibodies of the invention, particularly fragments that retain the antigen-binding activity of the antibodies. Such fragments include, but are not limited to, single chain antibodies, Fab, Fab', F(ab')₂, Fv or scFv. Although the specification, including the claims, may, in some places, refer explicitly to antigen binding fragment(s), antibody fragment(s), variant(s) and/or derivative(s) of antibodies, it is understood that the term "antibody" includes all categories of antibodies, namely, antigen binding fragment(s), antibody fragment(s), variant(s) and derivative(s) of antibodies.

As used herein, the terms "antigen binding fragment," "fragment," and "antibody fragment" are used interchangeably to refer to any fragment of an antibody of the invention that retains the antigen-binding activity of the antibody. Examples of antibody fragments include, but are not limited to, a single chain antibody, Fab, Fab', F(ab')₂, Fv or scFv. Fragments of the antibodies of the invention can be obtained from the antibodies by methods that include digestion with enzymes, such as pepsin or papain, and/or by cleavage of disulfide bonds by chemical reduction. Alternatively, fragments of the antibodies can be obtained by cloning and expression of part of the sequences of the heavy or light chains. Antibody "fragments" include Fab, Fab', F(ab')₂ and Fv fragments. The invention also encompasses single-chain Fv fragments (scFv) derived from the heavy and light chains of an antibody of the invention. For example, the invention includes a scFv comprising the CDRs from an antibody of the invention. Also included are heavy or light chain monomers and dimers, single domain heavy chain antibodies, single domain light chain antibodies, as well as single chain antibodies, e.g., single chain Fv in which the heavy and light chain variable domains are joined by a peptide linker.

Antibody fragments of the invention may impart monovalent or multivalent interactions and be contained in a variety of structures as described above. For instance, scFv molecules may be synthesized to create a trivalent "triabody" or a tetravalent "tetrabody". The scFv molecules may include a domain of the Fc region resulting in bivalent minibodies. In addition, the sequences of the invention may be a component of multispecific molecules in which the sequences of the invention target the epitopes of the invention and other regions of the molecule bind to other targets. Exemplary molecules include, but are not limited to, bispecific Fab2, trispecific Fab3, bispecific scFv, and diabodies (Holliger and Hudson, 2005, *Nature Biotechnology* 9: 1126-1136).

Antibodies according to the present invention may be provided in purified form. Typically, the antibody will be present in a composition that is substantially free of other polypeptides *e.g.*, where less than 90% (by weight), usually less than 60% and more usually less than 50% of the composition is made up of other polypeptides.

Antibodies according to the present invention may be immunogenic in human and/or in non-human (or heterologous) hosts *e.g.*, in mice. For example, the antibodies may have an idiotope that is immunogenic in non-human hosts, but not in a human host. Antibodies of the invention for human use include those that cannot be easily isolated from hosts such as mice, goats, rabbits, rats, non-primate mammals, etc. and cannot generally be obtained by humanization or from xeno-mice.

As used herein, a "neutralizing antibody" is one that can neutralize, *i.e.*, prevent, inhibit, reduce, impede or interfere with, the ability of a pathogen to initiate and/or perpetuate an infection in a host. The terms "neutralizing antibody" and "an antibody that neutralizes" or "antibodies that neutralize" are used interchangeably herein. These antibodies can be used alone, or in combination, as prophylactic or therapeutic agents upon appropriate formulation, in association with active vaccination, as a diagnostic tool, or as a production tool as described herein.

As used herein, the terms "nucleic acid", "nucleic acid molecule" and "polynucleotide" are used interchangeably and are intended to include DNA molecules and RNA molecules. A

nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

As used herein, the terms "cell," "cell line," and "cell culture" are used interchangeably and all such designations include progeny. Thus, the words "transformants" and "transformed cells" include the primary subject cell and cultures derived therefrom without regard for the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. Variant progeny that have the same function or biological activity as screened for in the originally transformed cell are included.

Where distinct designations are intended, it will be clear from the context.

Doses are often expressed in relation to the bodyweight. Thus, a dose which is expressed as [g, mg, or other unit]/kg (or g, mg etc.) usually refers to [g, mg, or other unit] "per kg (or g, mg etc.) bodyweight", even if the term "bodyweight" is not explicitly mentioned.

The terms "binding" and, in particular, "specifically binding" and similar reference does not encompass non-specific sticking.

The term "vaccine" as used herein is typically understood to be a prophylactic or therapeutic material providing at least one antigen, preferably an immunogen. The antigen or immunogen may be derived from any material that is suitable for vaccination. For example, the antigen or immunogen may be derived from a pathogen, such as from bacteria, virus particles or protozoa, parasites etc., or from a tumor or cancerous tissue. The antigen or immunogen can typically stimulate the body's adaptive immune system to provide an adaptive immune response. In particular, an "antigen" or an "immunogen" refers typically to a substance which may be recognized by the immune system, preferably by the adaptive immune system, and which is capable of triggering an antigen-specific immune response, e.g. by formation of antibodies and/or antigen-specific T cells as part of an adaptive immune response. Typically, an antigen may be or may comprise a peptide or protein which may be presented by the MHC to T-cells.

As used herein, "sequence variant" (also referred to as "variant") refers to any alteration in a reference sequence, whereby a reference sequence is any of the sequences listed in the "Tables of Sequences and SEQ ID Numbers" (sequence listing), i.e. SEQ ID NO: 1 to SEQ ID NO: 332. Thus, the term "sequence variant" includes nucleotide sequence variants and amino acid sequence variants. In particular, in a "sequence variant" the functionality (of the reference sequence) is preserved, i.e. the sequence variant is functional (also referred to as "functional sequence variant"). Sequence variants typically maintain the biological function of, for example, the antibody or an antigen/immunogen. In the context of the present invention such a maintained biological function is preferably the binding of the antibody to *P. falciparum* sporozoites, in particular to *Plasmodium* circumsporozoite protein (CSP) or the ability of a peptide/protein to elicit an immune response, in particular the production of antibodies.

Preferred sequence variants are thus functional sequence variants having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity to a reference sequence. The phrase "*functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity*", as used herein, means (i) that the sequence variant is functional as described herein and (ii) the higher the % sequence identity, the more preferred the sequence variant. In other words, the phrase "*functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity*", means in particular that the functional sequence variant has at least 70% sequence identity, preferably at least 75% sequence identity, preferably at least 80% sequence identity, more preferably at least 85% sequence identity, more preferably at least 88% sequence identity, even more preferably at least 90% sequence identity, even more preferably at least 92% sequence identity, still more preferably at least 95% sequence identity, still more preferably at least 96% sequence identity, particularly preferably at least 97% sequence identity, particularly preferably at least 98% sequence identity and most preferably at least 99% sequence identity to the respective reference sequence.

Sequence identity is usually calculated with regard to the full length of the reference sequence (i.e. the sequence recited in the application). Percentage identity, as referred to herein, can be determined, for example, using BLAST using the default parameters specified by the NCBI
5 (the National Center for Biotechnology Information; <http://www.ncbi.nlm.nih.gov/>) [Blosum 62 matrix; gap open penalty=11 and gap extension penalty=1].

A nucleotide "sequence variant" (i.e., a "sequence variant" of a nucleotide sequence) in the context of a nucleotide sequence has an altered sequence in which one or more of the
10 nucleotides in the reference sequence is deleted, or substituted, or one or more nucleotides are inserted into the sequence of the reference nucleotide sequence. Nucleotides are referred to herein by the standard one-letter designation (A, C, G, or T). Due to the degeneracy of the genetic code, a "sequence variant" of a nucleic acid (nucleotide) sequence can either result in a change in the respective reference amino acid sequence, i.e. in a "sequence variant" of
15 the respective amino acid sequence or not. Preferred sequence variants are such nucleotide sequence variants, which do not result in amino acid sequence variants (silent mutations), but other non-silent mutations are within the scope as well, in particular mutant nucleotide sequences, which result in an amino acid sequence, which is at least 70% identical to the reference sequence, preferably at least 80% identical to the reference sequence, more
20 preferably at least 90% identical, even more preferably at least 95% identical, and particularly preferably at least 99% identical to the reference sequence.

An amino acid "sequence variant" (i.e., a "sequence variant" of an amino acid sequence) in the context of an amino acid has an altered sequence in which one or more of the amino
25 acids in the reference sequence is deleted or substituted, or one or more amino acids are inserted into the sequence of the reference amino acid sequence. As a result of the alterations, the amino acid sequence variant has an amino acid sequence which is at least 70% identical to the reference sequence, preferably at least 80% identical to the reference sequence, more preferably at least 90% identical, even more preferably at least 95% identical, and particularly
30 preferably at least 99% identical to the reference sequence. Variant sequences which are at least 90% identical have no more than 10 alterations, i.e. any combination of deletions, insertions or substitutions, per 100 amino acids of the reference sequence.

In the context of peptides/proteins, a "linear sequence" or a "sequence" is the order of amino acids in a peptide/protein in an amino to carboxyl terminal direction in which residues that neighbor each other in the sequence are contiguous in the primary structure of the peptide/protein.

While it is possible to have non-conservative amino acid substitutions in a "sequence variant", it is preferred in a "sequence variant" that the substitutions are conservative amino acid substitutions, in which the substituting amino acid has similar structural and/or chemical properties as the corresponding substituted amino acid (i.e. the amino acid in the original sequence which was substituted). By way of example, conservative amino acid substitutions involve substitution of one aliphatic or hydrophobic amino acid, e.g. alanine, valine, leucine and isoleucine, with another; substitution of one hydroxyl-containing amino acid, e.g. serine and threonine, with another; substitution of one acidic residue, e.g. glutamic acid or aspartic acid, with another; replacement of one amide-containing residue, e.g. asparagine and glutamine, with another; replacement of one aromatic residue, e.g. phenylalanine and tyrosine, with another; replacement of one basic residue, e.g. lysine, arginine and histidine, with another; and replacement of one small amino acid, e.g., alanine, serine, threonine, methionine, and glycine, with another.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include the fusion to the N- or C-terminus of an amino acid sequence to a reporter molecule or an enzyme.

Importantly, the sequence variants are usually functional sequence variants, i.e. the alterations in the sequence variants do not abolish the functionality of the respective reference sequence as described above. Guidance in determining which nucleotides and amino acid residues, respectively, may be substituted, inserted or deleted without abolishing such functionality are found by using computer programs well known in the art.

As used herein, a nucleic acid sequence or an amino acid sequence "derived from" a designated nucleic acid, peptide, polypeptide or protein refers to the origin of the nucleic acid, peptide, polypeptide or protein. Preferably, the nucleic acid sequence or amino acid sequence which is derived from a particular sequence has an amino acid sequence that is essentially identical to that sequence or a portion thereof, from which it is derived, whereby "essentially identical" includes sequence variants as defined above. Preferably, the nucleic acid sequence or amino acid sequence which is derived from a particular peptide or protein, is derived from the corresponding domain in the particular peptide or protein. Thereby, "corresponding" refers in particular to the same functionality. For example, an "extracellular domain" corresponds to another "extracellular domain" (of another protein), or a "transmembrane domain" corresponds to another "transmembrane domain" (of another protein). "Corresponding" parts of peptides, proteins and nucleic acids are thus easily identifiable to one of ordinary skill in the art. Likewise, sequences "derived from" other sequence are usually easily identifiable to one of ordinary skill in the art as having its origin in the sequence.

Preferably, a nucleic acid sequence or an amino acid sequence derived from another nucleic acid, peptide, polypeptide or protein may be identical to the starting nucleic acid, peptide, polypeptide or protein (from which it is derived). However, a nucleic acid sequence or an amino acid sequence derived from another nucleic acid, peptide, polypeptide or protein may also have one or more mutations relative to the starting nucleic acid, peptide, polypeptide or protein (from which it is derived), in particular a nucleic acid sequence or an amino acid sequence derived from another nucleic acid, peptide, polypeptide or protein may be a functional sequence variant as described above of the starting nucleic acid, peptide, polypeptide or protein (from which it is derived). For example, in a peptide/protein one or more amino acid residues may be substituted with other amino acid residues or one or more amino acid residue insertions or deletions may occur.

As used herein, the term "mutation" relates to a change in the nucleic acid sequence and/or in the amino acid sequence in comparison to a reference sequence, e.g. a corresponding genomic sequence. A mutation, e.g. in comparison to a genomic sequence, may be, for example, a (naturally occurring) somatic mutation, a spontaneous mutation, an induced

mutation, e.g. induced by enzymes, chemicals or radiation, or a mutation obtained by site-directed mutagenesis (molecular biology methods for making specific and intentional changes in the nucleic acid sequence and/or in the amino acid sequence). Thus, the terms "mutation" or "mutating" shall be understood to also include physically making a mutation, e.g. in a nucleic acid sequence or in an amino acid sequence. A mutation includes substitution, deletion and insertion of one or more nucleotides or amino acids as well as inversion of several successive nucleotides or amino acids. To achieve a mutation in an amino acid sequence, preferably a mutation may be introduced into the nucleotide sequence encoding said amino acid sequence in order to express a (recombinant) mutated polypeptide. A mutation may be achieved e.g., by altering, e.g., by site-directed mutagenesis, a codon of a nucleic acid molecule encoding one amino acid to result in a codon encoding a different amino acid, or by synthesizing a sequence variant, e.g., by knowing the nucleotide sequence of a nucleic acid molecule encoding a polypeptide and by designing the synthesis of a nucleic acid molecule comprising a nucleotide sequence encoding a variant of the polypeptide without the need for mutating one or more nucleotides of a nucleic acid molecule.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

It is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

The present invention is based, amongst other findings, on the surprising finding of extremely potent antibodies binding to malaria circumsporozoite protein (CSP). In particular, those

antibodies were surprisingly found to bind to an epitope on the malaria circumsporozoite protein, which is located in/spanning the junction between the N-terminus and the NANP-repeats, close to the functionally important Region I. Interestingly, that region is not included in the currently only approved malaria vaccine RTS,S/AS01.

5

Peptide comprising or consisting of the amino acid according to SEQ ID NO: 1

10 In a first aspect the present invention provides a peptide comprising or consisting of the amino acid according to SEQ ID NO: 1:

NPDP

[SEQ ID NO: 1]

15 This motif can be found in the Plasmodium circumsporozoite protein C-terminally of region I and N-terminally of the NANP-repeats. Surprisingly it was found that antibodies binding to that motif according to SEQ ID NO: 1 are extremely potent and significantly reduce liver parasite burden (of Plasmodium sporozoites) *in vivo*, indicating the ability of such antibodies to potently inhibit (i) sporozoite invasion and (ii) liver stage parasite multiplication *in vivo*.
20 Since the peptide according to the present invention is able to give rise to such potent antibodies, it is useful, for example, to generate a potent vaccine against malaria, which leads to inhibition of (i) sporozoite invasion and (ii) liver stage parasite multiplication *in vivo*. Thereby, not only the disease in an individual can be prevented and/or treated, but also the spreading of the disease in a population can be inhibited.

25

Preferably, the peptide according to the present invention comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 2 – 5, preferably the peptide comprises the amino acid sequence according to SEQ ID NO: 5.

30 For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 2:

NPDPN

[SEQ ID NO: 2]

For example, the peptide according to the present invention preferably comprises or consists
5 of an amino acid sequence according to SEQ ID NO: 3:

NPDPNA

[SEQ ID NO: 3]

10 For example, the peptide according to the present invention preferably comprises or consists
of an amino acid sequence according to SEQ ID NO: 4:

NPDPNAN

[SEQ ID NO: 4]

15

More preferably, the peptide according to the present invention comprises or consists of an
amino acid sequence according to SEQ ID NO: 5:

NPDPNANP

20 [SEQ ID NO: 5]

Such a peptide according to SEQ ID NO: 5 comprises, in addition to the motif according to
SEQ ID NO: 1, the first "NANP"-sequence (i.e. the very N-terminal part of the NANP-repeats).

25 Moreover, the peptide according to the present invention may preferably comprise or consist
of an amino acid sequence according to any of SEQ ID NOs: 6 – 22.

For example, the peptide according to the present invention preferably comprises or consists
of an amino acid sequence according to SEQ ID NO: 6:

30

NPDPNANPN

[SEQ ID NO: 6]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 7:

5 GNPDPNANP
[SEQ ID NO: 7]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 8:

10 GNPDPNANPN
[SEQ ID NO: 8]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 9:

15 DGNPDPNANP
[SEQ ID NO: 9]

20 For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 10:

NPDPNANPNK
[SEQ ID NO: 10]

25 For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 11:

30 DGNPDPNANPN
[SEQ ID NO: 11]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 12:

GNPDPNANPNK

5 [SEQ ID NO: 12]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 13:

10 DGNPDPNANPNK

[SEQ ID NO: 13]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 14:

15

ADGNPDPNANPN

[SEQ ID NO: 14]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 15:

20

QPADGNPDPNANPNK

[SEQ ID NO: 15]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 16:

25

ADGNPDPNANPNK

[SEQ ID NO: 16]

30

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 17:

PADGNPDPNANPNK

[SEQ ID NO: 17]

5

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 18:

ADGNPDPNANPNKN

10 [SEQ ID NO: 18]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 19:

15 PADGNPDPNANPNKN

[SEQ ID NO: 19]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 20:

20

QPADGNPDPNANPNKN

[SEQ ID NO: 20]

For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 21:

25

PADGNPDPNANPNKNN

[SEQ ID NO: 21]

30 For example, the peptide according to the present invention preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 22:

QPADGNPDPNANPNKNN

[SEQ ID NO: 22]

5 More preferably, the peptide according to the present invention comprises or consists of an amino acid sequence according to SEQ ID NO: 23 or sharing at least 72%, preferably at least 77%, more preferably at least 83%, even more preferably at least 88%, most preferably at least 94% sequence identity with SEQ ID NO. 23.

KQPADGNPDPNANPNKNN

10 [SEQ ID NO: 23]

In general, the peptide according to the present invention preferably consists of a fragment of *Plasmodium* circumsporozoite protein (CSP), more preferably of a fragment of *Plasmodium falciparum* circumsporozoite protein, or, preferably, shares at least 70%, preferably at least 80%, more preferably at least 90%, even more preferably at least 95%, most preferably at least 98% sequence identity with a fragment of *Plasmodium* circumsporozoite protein (over the entire length of the peptide according to the present invention), more preferably with a fragment of *Plasmodium falciparum* circumsporozoite protein (over the entire length of the peptide according to the present invention). In other words, the peptide preferably either
20 consists of a fragment of *Plasmodium* circumsporozoite protein (CSP), more preferably of a fragment of *Plasmodium falciparum* circumsporozoite protein, or of a (functional) sequence variant thereof as described herein. This means that a particularly preferred peptide (i) comprises a "core" motif according to any of SEQ ID NOs 1 – 23 as described above, wherein core motifs according to SEQ ID NOs 1 or 5 are particularly preferred, and (ii) "outside" the
25 core motif the peptide is still a sequence variant of CSP as described herein. To this end, sequence identity is calculated over the complete length of the peptide in comparison to a (corresponding) CSP fragment as reference sequence. A preferred CSP reference sequence is the amino acid sequence according to SEQ ID NO: 24. Accordingly, the fragment of *Plasmodium* circumsporozoite protein (as referred to above) is preferably a fragment of SEQ
30 ID NO: 24. The fragment of *Plasmodium (falciparum)* circumsporozoite protein (CSP), as referred to above, has preferably a length of at least 8 or 10 amino acids, preferably at least 15 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids,

more preferably at least 30 amino acids, more preferably at least 40 amino acids, even more preferably at least 50 amino acids, even more preferably at least 75 amino acids, even more preferably at least 100 amino acids, still more preferably at least 150 amino acids, still more preferably at least 200 amino acids, most preferably at least 300 amino acids.

5

Preferably, the peptide according to the present invention has a length of no more than 380 amino acids, preferably of no more than 350 amino acids, preferably of no more than 320 amino acids, more preferably of no more than 300 amino acids, more preferably of no more than 275 amino acids, more preferably of no more than 250 amino acids, even more preferably of no more than 225 amino acids, even more preferably of no more than 200 amino acids, even more preferably of no more than 200 amino acids, even more preferably of no more than 175 amino acids, still more preferably of no more than 150 amino acids, still more preferably of no more than 125 amino acids, still more preferably of no more than 100 amino acids, particularly preferably of no more than 75 amino acids, and most preferably of no more than 50 amino acids.

15

More preferably, the peptide according to the present invention has a length from 4 to 380 amino acids, preferably the peptide has a length from 5 to 350 amino acids, preferably the peptide has a length from 5 to 300 amino acids, preferably the peptide has a length from 5 to 250 amino acids, more preferably the peptide has a length from 5 to 200 amino acids, more preferably the peptide has a length from 5 to 150 amino acids, more preferably the peptide has a length from 5 to 100 amino acids, even more preferably the peptide has a length from 6 to 80 amino acids, even more preferably the peptide has a length from 7 to 70 amino acids, even more preferably the peptide has a length from 8 to 60 amino acids, still more preferably the peptide has a length from 9 to 50 amino acids, still more preferably the peptide has a length from 10 to 40 amino acids, still more preferably the peptide has a length from 11 to 30 amino acids, most preferably the peptide has a length from 12 to 25 amino acids.

20

25

The peptide according to any one of the previous claims, wherein the peptide is a recombinant peptide. A recombinant peptide is a peptide, which does not occur in nature. For example, the peptide may be modified as described herein, such that the resulting modified peptide is a peptide, which does not occur in nature. This may be achieved either

30

by a non-natural (or synthetic) modification or by a modification, which does in nature not occur at the peptide according to the present invention. Alternatively or additionally, the recombinant peptide may also differ in its length from peptides occurring in nature.

- 5 Moreover, the peptide preferably includes one or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly one or (ii) one or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present
- 10 invention comprises (i) exactly two or (ii) two or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly three or (ii) three or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present
- 15 invention comprises (i) exactly four or (ii) four or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly five or (ii) five or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present
- 20 invention comprises (i) exactly six or (ii) six or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly seven or (ii) seven or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present
- 25 invention comprises (i) exactly eight or (ii) eight or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly nine or (ii) nine or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present
- 30 invention comprises (i) exactly ten or (ii) ten or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly eleven or (ii) eleven or

more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present invention comprises (i) exactly twelve or (ii) twelve or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly thirteen or (ii) thirteen or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present invention comprises (i) exactly fourteen or (ii) fourteen or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly fifteen or (ii) fifteen or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present invention comprises (i) exactly sixteen or (ii) sixteen or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly seventeen or (ii) seventeen or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present invention comprises (i) exactly eighteen or (ii) eighteen or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). Preferably, the peptide according to the present invention comprises (i) exactly nineteen or (ii) nineteen or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP). It is also preferred that the peptide according to the present invention comprises (i) exactly twenty or (ii) twenty or more mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP).

Preferably, the peptide according to the present invention comprises 1, 2, 3, 4, or 5 mutations in comparison to the corresponding reference fragment of *Plasmodium* circumsporozoite protein (CSP), more preferably in comparison to the corresponding reference fragment of SEQ ID NO: 24.

The peptide according to the present invention is preferably for use in the prevention and/or treatment of malaria as described herein. In other words, it is preferred that the peptide according to the present invention is used for the manufacture of a medicament, preferably for the prevention and/or treatment of malaria as described herein.

5

Protein comprising the peptide according to the invention, virus-like particle and protein nanoparticle

10 In a further aspect the present invention provides a protein comprising the peptide according to the present invention. Accordingly, the protein may consist of the peptide according to the present invention. However, it is preferred that the protein comprises (i) the peptide according to the present invention and (ii) an additional amino acid sequence, preferably providing a synergistic functionality and/or an additional functionality to the protein. In other words, such
15 an additional amino acid sequence may preferably provide a functionality, in addition to the peptide's functionality (as immunogen/antigen), which is preferably synergistic with to the peptide's functionality (as immunogen/antigen). Non-limiting examples of such functionalities include (i) targeting, e.g. as described below, and (ii) immunogenicity, e.g. as described below.

20

To this end, the protein according to the present invention is preferably a fusion protein. Fusion proteins typically comprise two or more distinct functionalities. Accordingly, fusion proteins typically comprise "parts" from different sources, for example a fusion protein comprises distinct proteins/peptides encoded by at least two distinct genes or parts of (distinct)
25 genes. Accordingly, fusion proteins may be also referred to as "chimeric proteins". Even though fusion proteins may, in general, occur in nature, e.g., when a complex mutation, such as a chromosomal translocation, tandem duplication, or retrotransposition creates a novel coding sequence containing parts of the coding sequences from two different genes (for example in cancer cells), recombinant fusion proteins (which do not occur in nature) are
30 preferred. Recombinant fusion proteins do not occur in nature in that combination.

For example, the protein according to the present invention may comprise – in addition to the peptide according to the present invention HBsAg or a fragment of HBsAg. HBsAg is the surface antigen of the hepatitis B virus (HBV).

5 The hepatitis B virus (HBV) consists of (i) an envelope containing three related surface proteins (hepatitis B surface antigen, HBsAg) and lipid and (ii) an icosahedral nucleocapsid enclosing the viral DNA genome and DNA polymerase. The HBV capsid is formed in the cytosol of the infected cell during packaging of an RNA pregenome replication complex and gains the ability to bud during synthesis of the viral DNA genome by reverse transcription of the pregenome in the lumen of the particle. The three HBV envelope proteins S-HBsAg, M-HBsAg, and L-HBsAg shape a complex transmembrane fold at the endoplasmic reticulum,
10 and form disulfide-linked homo- and heterodimers.

A “fragment” of HBsAg typically has a length of at least 5, preferably at least 10 amino acids, preferably at least 15 amino acids, preferably at least 20 amino acids, more preferably at least
15 25 amino acids, more preferably at least 30 amino acids, more preferably at least 40 amino acids, even more preferably at least 50 amino acids, even more preferably at least 75 amino acids, still more preferably at least 100 amino acids, still more preferably at least 150 amino acids, most preferably at least 200 amino acids. In other words, the longer the fragment, the more preferred.

20

For example, the fragment of HBsAg may at least contain the antigenic loop region of HBsAg. The envelope of the hepatitis B virus contains three “HBV envelope proteins” (also known as “HBsAg”, “hepatitis B surface antigen”): S protein (for “small”, also referred to as S-HBsAg), M protein (for “middle”, also referred to as M-HBsAg) and L protein (for “large”, also referred
25 to as L-HBsAg). S-HBsAg, M-HBsAg and L-HBsAg share the same C-terminal extremity (also referred to as “S domain”, 226 amino acids), which corresponds to the S protein (S-HBsAg) and which is crucial for virus assembly and infectivity. S-HBsAg, M-HBsAg and L-HBsAg are synthesized in the endoplasmic reticulum (ER), assembled, and secreted as particles through the Golgi apparatus. The S domain comprises four predicted transmembrane (TM) domains,
30 whereby both, the N-terminus as well as the C-terminus of the S domain are exposed to the lumen. The transmembrane domains TM1 and TM2 are both necessary for cotranslational protein integration into the ER membrane and the transmembrane domains TM3 and TM4 are

located in the C-terminal third of the S domain. The “antigenic loop region” of HBsAg is located between the predicted TM3 and TM4 transmembrane domains of the S domain of HBsAg, whereby the antigenic loop region comprises amino acids 101 – 172 of the S domain, which contains 226 amino acids in total (Salisse J. and Sureau C., 2009, Journal of Virology 83: 9321-9328). It is important to note that a determinant of infectivity resides in the antigenic loop region of HBV envelope proteins. In particular, residues between 119 and 125 of the HBsAg contained a CXXC motif, which had been demonstrated to be the most important sequence required for the infectivity of HBV and HDV (Jaoude GA, Sureau C, Journal of Virology, 2005;79:10460–6).

Preferably, the protein according to the present invention comprises the S domain of HBsAg or a sequence variant thereof as described herein. More preferably, the protein according to the present invention comprises SEQ ID NO: 319 or a sequence variant thereof as described herein:

MENITSGFLGPLLVLQAGFFLLTRILTIPQSLDSWWTSNLNGLGGTTVCLGQNSQSPTS NHSPSTSC
PPTCPGYRWMCLRRFIIFLLFILLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCMTTAQGTS
MYPSCCCTKPSDGNCTCIPISSWAFGKFLWEWASARFSWLSLLVPFVQWFVGLSPTVWLSVI
WMMWYWGPSLYSILSPFLPLLPIFFCLWVYI

(SEQ ID NO: 319)

SEQ ID NO: 319 shows an exemplified amino acid sequence of an S domain of HBsAg.

Preferably, the protein according to the present invention further comprises targeting moiety, such as a targeting peptide. In general, a targeting peptide is peptide chain that directs the transport of a protein to a specific location, for example to a specific cell type, into cells or to a specific region in the cell, including the nucleus, mitochondria, endoplasmic reticulum (ER), chloroplast, apoplast, peroxisome and plasma membrane. Targeting peptides may optionally be cleaved from the protein, e.g. by signal peptidases, after the proteins are transported to the specific location. Preferred targeting peptides include antibodies and fragments thereof, such as scFV. For example, such antibodies or antibody fragments may be directed to surface molecules of specific cell types.

For example, the targeting peptide may have a length of no more than 1000 amino acids, preferably of no more than 500 amino acids, more preferably of no more than 200 amino acids, even more preferably of no more than 100 amino acids, still more preferably of no more than 80 amino acids, particularly preferably of no more than 70 amino acids and most preferably of no more than 50 amino acids. For example, the targeting peptide may have a length from 3 to 70 amino acids.

Preferably the targeting moiety, in particular the targeting peptide, targets the protein according to the present invention to a specific cell type. More preferably, the targeting moiety, in particular the targeting peptide, targets the protein according to the present invention to antigen-presenting cells, such as to dendritic cells. An antigen-presenting cell (APC) typically displays an antigen complexed with major histocompatibility complexes (MHCs) on their surfaces; a process known as "antigen presentation". T cells may recognize these complexes using their T cell receptors (TCRs). Accordingly, APCs process antigens and present them to T-cells. Antigen-presenting cells are vital for effective adaptive immune response, as the functioning of both cytotoxic and helper T cells is dependent on APCs. Antigen presentation allows for specificity of adaptive immunity and can contribute to immune responses against both intracellular and extracellular pathogens.

Preferably, the targeted APC is a professional APC. Professional antigen-presenting cells specialize in presenting antigen to T cells and are very efficient at internalizing antigens, for example by phagocytosis (macrophages and dendritic cells) or by receptor-mediated endocytosis (B cells), processing the antigen into peptide fragments and then displaying those peptides, bound to a class II MHC molecule, on their membrane. Preferred examples of APCs to be targeted include macrophages, B cells and dendritic cells.

Most preferably, the targeted APC is a dendritic cell (DC). Dendritic cells have the broadest range of antigen presentation and are necessary for activation of naive T cells. DCs present antigen to both helper and cytotoxic T cells. They can also perform cross-presentation, a process by which they present an exogenous antigen on MHC class I molecules to cytotoxic T cells. Cross-presentation allows for the activation of these T cells. Dendritic cells may be

recognized by a targeting moiety, such as a targeting peptide, by their specific receptors including DEC-205, Clec9A and Clec12A.

Preferably, the targeting moiety, in particular the targeting peptide, targets DEC-205. DEC-205 is a type I cell surface protein expressed by dendritic cells (DC). Targeting of DEC-205 may be achieved by DEC-205 antibodies or fragments thereof, such as anti-DEC-205scFv, for example as described in Birkholz K. et al., 2010, Blood 116(13):2277-85 (however, with the peptide according to the present invention as antigen/epitope).

It is also preferred that the targeting moiety, in particular the targeting peptide, targets Clec9A. Clec9A is a group V C-type lectin-like receptor (CTLR) that functions as an activation receptor and is expressed on myeloid lineage cells. In humans, this receptor is selectively expressed by BDCA3(+) myeloid dendritic cells (mDCs), which have been proposed to be the main human cross-presenting mDCs and may represent the human homologue of murine CD8(+) DCs. Targeting of Clec9A may be achieved by a Clec9A antibodies or fragments thereof, for example as described in Huysamen C. et al., 2008, J. Biol. Chem. 283(24):16693-16701 or in Schreibelt G. et al., 2012, Blood 119(10):2284-92.

Preferably, the targeting moiety, in particular the targeting peptide, targets Clec12A. Clec12A (also known as CD371 DCAL-2, MICL or CLL-1), is a 30 kD type II transmembrane protein with extracellular C-type lectin domains, which belongs to the C-type lectin family. Targeting of Clec12A may be achieved by a Clec12A antibodies or fragments thereof, for example as described in Hutten T.J.A. et al., 2016, J. Immunol. 197 (7) 2715-2725.

Accordingly, it is preferred that the targeting moiety, in particular the targeting peptide, targets DEC-205, Clec9A and/or Clec12A. Thereby, the protein is typically directed to dendritic cells, which may then process the protein and present the antigen/immunogen, such as the peptide according to the present invention, in order to trigger an immune response.

It is also preferred that the targeting moiety, in particular the targeting peptide, targets the protein to hepatocytes. To this end, the targeting moiety, in particular the targeting peptide,

may comprise, for example, an antibody or a fragment thereof, directed against any specific hepatocyte surface molecule.

It is also preferred that the targeting moiety, in particular the targeting peptide, comprises an N-terminal region of *Plasmodium* circumsporozoite protein, in particular of a *Plasmodium falciparum* circumsporozoite protein. In this context, an N-terminal region of *Plasmodium* circumsporozoite protein may be any fragment of the N-terminus of CSP (wherein the "N-terminus of CSP" extends until the central repeat region/NANP-repeat region of CSP; i.e. the "N-terminus of CSP" refers to all amino acids N-terminal of the central repeat region/NANP-repeat region of CSP), or a sequence variant thereof as described herein. A fragment of the N-terminus of CSP typically has a length of at least 3 amino acids, preferably at least 5 amino acids, more preferably at least 8 amino acids, even more preferably at least 10 amino acids, still more preferably at least 12 amino acids, particularly preferably at least 15 amino acids and most preferably at least 20 amino acids. Preferred fragments and sequence variants thereof provide targeting to hepatocytes. A preferred example of an "N-terminus of CSP" is shown in SEQ ID NO: 320:

MMRKLAILSVSSFLFVEALFQEYQCYGSSNTRVLNELNYDNAGTNLYNELEMNYYGKQENW
YSLKKNSRSLGENDDGNNEDNEKLRKPKHKKLKQPADGNPDP

(SEQ ID NO: 320)

Particularly preferably, the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of CSP region I, in particular the N-terminal region of *Plasmodium* circumsporozoite protein thus comprises or consists of an amino acid sequence according to SEQ ID NO: 25.

It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of an amino acid sequence according to SEQ ID NO: 321 or of a sequence variant thereof as described herein:

KKLKQPA
(SEQ ID NO: 321)

It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of an amino acid sequence according to SEQ ID NO: 322 or of a sequence variant thereof as described herein:

5

HKKLKQPAD
(SEQ ID NO: 322)

It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of an amino acid sequence according to SEQ ID NO: 323 or of a sequence variant thereof as described herein:

10

KHKKLKQPADG
(SEQ ID NO: 323)

15

Moreover, the N-terminal region of *Plasmodium* circumsporozoite protein preferably comprises or consists of an amino acid sequence according to SEQ ID NO: 324 or of a sequence variant thereof as described herein:

20 KHKKLKQP
(SEQ ID NO: 324)

It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of an amino acid sequence according to SEQ ID NO: 325 or of a sequence variant thereof as described herein:

25

RKPKHKKLKQP
(SEQ ID NO: 325)

30 It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of an amino acid sequence according to SEQ ID NO: 326 or of a sequence variant thereof as described herein:

PKHKKLKQPADGN
(SEQ ID NO: 326)

- 5 It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of an amino acid sequence according to SEQ ID NO: 327 or of a sequence variant thereof as described herein:

KPKHKKLKQPADGNP
10 (SEQ ID NO: 327)

It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of an amino acid sequence according to SEQ ID NO: 328 or of a sequence variant thereof as described herein:

15
RKPKHKKLKQPADGNPD
(SEQ ID NO: 328)

- It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein
20 comprises or consists of an amino acid sequence according to SEQ ID NO: 329 or of a sequence variant thereof as described herein:

NEKLRKPKHKKLKQP
(SEQ ID NO: 329)

- 25
It is also preferred that the N-terminal region of *Plasmodium* circumsporozoite protein comprises or consists of an amino acid sequence according to SEQ ID NO: 330 or of a sequence variant thereof as described herein:

30 NEKLRKPKHKKLKQPADG
(SEQ ID NO: 330)

Preferably, the protein according to the present invention further comprises an immunogenic peptide. In general, an immunogenic peptide increases the immunogenicity of the peptide according to the present invention. To this end, an immunogenic peptide is, by itself, immunogenic, i.e. able to elicit an immune response. For example, an immunogenic peptide may comprise an antigen/immunogen distinct from the peptide according to the present invention, such as HBsAg as described above. Many immunogenic peptides are known in the art. Moreover, it is well known to the skilled person how immunogenic peptides can be designed, for example as described in Flower D.R., 2013, Nature Chemical Biology 9(12): 749–753: Designing immunogenic peptides.

The protein according to the present invention may further comprise linker sequences, as known in the art, for example “GS-linkers”.

The protein according to the present invention has preferably a length of at least 20 amino acids, preferably at least 50 amino acids, preferably at least 60 amino acids, more preferably at least 70 amino acids, more preferably at least 80 amino acids, more preferably at least 90 amino acids, even more preferably at least 100 amino acids, even more preferably at least 150 amino acids, even more preferably at least 200 amino acids, still more preferably at least 250 amino acids, still more preferably at least 300 amino acids, most preferably at least 350 or at least 400 amino acids.

In a further aspect the present invention also provides a virus-like particle comprising the peptide according to the present invention as described herein or the protein according to the present invention as described herein.

As used herein, a “virus-like particle” (also “VLP”) refers in particular to a non-replicating, viral shell, derived from any of several viruses. VLPs are generally composed of one or more viral proteins, such as, but not limited to, those proteins referred to as capsid, coat, shell, surface and/or envelope proteins, or particle-forming polypeptides derived from these proteins. VLPs can form spontaneously upon recombinant expression of the protein in an appropriate expression system. Methods for producing particular VLPs are known in the art.

The presence of VLPs following recombinant expression of viral proteins can be detected using conventional techniques known in the art, such as by electron microscopy, biophysical characterization, and the like. Further, VLPs can be isolated by known techniques, e.g., density gradient centrifugation and identified by characteristic density banding. See, for
5 example, Baker et al. (1991) *Biophys. J.* 60: 1445-1456; and Hagensee et al. (1994) *J. Viral.* 68:4503-4505; Vincente, *J Invertebr Pathol.*, 2011; Schneider-Ohrum and Ross, *Curr. Top. Microbiol. Immunol.*, 354: 53073, 2012).

For example, if HBsAg or another viral protein is present at sufficient concentrations, virus-
10 like particles spontaneously assemble without DNA, resulting in a noninfectious immunogenic construct. Coadministration enables activation of the immune system and increases antibody response to the peptide according to the present invention.

A virus-like particle comprising the peptide according to the present invention or the protein
15 according to the present invention as described herein is thus in particular a virus-like particle (VLP) that includes the peptide or the protein according to the present invention, which comprises SEQ ID NO: 1. Preferred embodiments of the VLP comprising the peptide according to the present invention or the protein according to the present invention correspond to preferred embodiments of the the peptide according to the present invention
20 or the protein according to the present invention.

In general, VLPs lack the viral components that are required for virus replication and thus represent a highly attenuated form of a virus. The VLP can display a polypeptide (e.g., the peptide according to the present invention or the protein according to the present invention)
25 that is capable of eliciting an immune response to *Plasmodium* when administered to a subject. Virus like particles and methods of their production are known and familiar to the person of ordinary skill in the art, and viral proteins from several viruses are known to form VLPs, including human papillomavirus, HIV (Kang et al., *Biol. Chem.* 380: 353-64 (1999)), Semliki-Forest virus (Notka et al., *Biol. Chem.* 380: 341-52 (1999)), human polyomavirus
30 (Goldmann et al., *J. Virol.* 73: 4465-9 (1999)), rota virus (Jiang et al., *Vaccine* 17: 1005-13 (1999)), parvovirus (Casal, *Biotechnology and Applied Biochemistry*, Vol 29, Part 2, pp 141-150 (1999)), canine parvovirus (Hurtado et al., *J. Viral.* 70: 5422-9 (1996)), hepatitis E virus

(Li et al., J. Viral. 71: 35 7207-13 (1997)), and Newcastle disease virus. For example, a chimeric VLP containing the peptide according to the present invention can be a HBsAg-based VLP. The formation of such VLPs can be detected by any suitable technique. Examples of suitable techniques known in the art for detection of VLPs in a medium include, e.g.,
5 electron microscopy techniques, dynamic light scattering (DLS), selective chromatographic separation (e.g., ion exchange, hydrophobic interaction, and/or size exclusion chromatographic separation of the VLPs) and density gradient centrifugation.

In a further aspect the present invention also provides a protein nanoparticle comprising the
10 peptide according to the present invention or the protein according to the present invention.

As used herein, a "protein nanoparticle" refers in particular to a multi-subunit, protein-based polyhedron shaped structure. The subunits are each composed of proteins or polypeptides (for example a glycosylated polypeptide), and, optionally of single or multiple features of the
15 following: nucleic acids, prosthetic groups, organic and inorganic compounds. Non-limiting examples of protein nanoparticles include ferritin nanoparticles (see, e.g., Zhang, Y. *Int. J. Mol. Sci.*, 12:5406-5421, 2011, incorporated by reference herein), encapsulin nanoparticles (see, e.g., Sutter *et al.*, *Nature Struct. and Mol. Biol.*, 15:939-947, 2008, incorporated by reference herein), Sulfur Oxygenase Reductase (SOR) nanoparticles (see, e.g., Urich *et al.*,
20 *Science*, 311 :996-1000, 2006, incorporated by reference herein), lumazine synthase nanoparticles (see, e.g., Zhang *et al.*, *J. Mol. Biol.*, 306: 1099-1114, 2001) or pyruvate dehydrogenase nanoparticles (see, e.g., Izard et al., *PNAS* 96: 1240-1245, 1999, incorporated by reference herein). Ferritin, encapsulin, SOR, lumazine synthase, and pyruvate dehydrogenase are monomeric proteins that self-assemble into globular protein complexes
25 that in some cases consists of 24, 60, 24, 60, and 60 protein subunits, respectively. Preferably, ferritin, encapsulin, SOR, lumazine synthase, or pyruvate dehydrogenase monomers are linked to the peptide according to the present invention or to the protein according to the present invention and self-assembled into a protein nanoparticle presenting the disclosed antigen/epitope on its surface, which can be administered to a subject to stimulate an immune
30 response to the peptide according to the present invention or to the protein according to the present invention.

A protein nanoparticle comprising the immunogen according to the present invention as described herein is thus in particular a protein nanoparticle that includes the peptide according to the present invention or the protein according to the present invention. Preferred embodiments of the protein nanoparticle comprising the peptide according to the present invention or the protein according to the present invention correspond to preferred
5 embodiments of the peptide according to the present invention or of the protein according to the present invention.

For example, the protein nanoparticle may include one or more of any of the disclosed
10 peptides, wherein the protein nanoparticle preferably specifically binds to an antibody according to the present invention as described herein.

Non-limiting example of nanoparticles include ferritin nanoparticles, encapsulin nanoparticles and Sulfur Oxygenase Reductase (SOR) nanoparticles, which are comprised of
15 an assembly of monomeric subunits including ferritin proteins, encapsulin proteins and SOR proteins, respectively. To construct protein nanoparticles including the peptide according to the present invention or the protein according to the present invention, the peptide according to the present invention or the protein according to the present invention is usually linked to a subunit of the protein nanoparticle (such as a ferritin protein, an encapsulin protein or a
20 SOR protein). The fusion protein self-assembles into a nanoparticle under appropriate conditions.

Preferably, the protein nanoparticle is thus a ferritin nanoparticle, an encapsulin nanoparticle, a Sulfur Oxygenase Reductase (SOR) nanoparticle, a lumazine synthase nanoparticle or a
25 pyruvate dehydrogenase nanoparticle. More preferably, the protein nanoparticle is a ferritin nanoparticle.

Ferritin nanoparticles and their use for immunization purposes (e.g., for immunization against influenza antigens) has been disclosed in the art (see, e.g., Kanekiyo et al., Nature, 499: 102-
30 106, 2013, incorporated by reference herein in its entirety). Accordingly, a preferred protein nanoparticle is a ferritin nanoparticle. For example, any of the disclosed immunogens (in particular the peptide according to the present invention or the protein according to the

present invention) may be linked to a ferritin polypeptide or hybrid of different ferritin polypeptides to construct a ferritin protein nanoparticle. Accordingly, the protein nanoparticle comprising the peptide according to the present invention or the protein according to the present invention is preferably a ferritin nanoparticle.

5

Ferritin is a globular protein that is found in all animals, bacteria, and plants, and which acts primarily to control the rate and location of polynuclear $\text{Fe(III)}_2\text{O}_3$ formation through the transportation of hydrated iron ions and protons to and from a mineralized core. The globular form of ferritin is made up of monomeric subunits, which are polypeptides having a molecule weight of approximately 17-20 kDa. An example of the sequence of one such monomeric subunit is represented by SEQ ID NO: 331:

10

ferritin polypeptide:

MLSKDIKLLNEQVNKEMNSSNLYMSMSSWCYTHSLDGAGLFLFDHAAEEYEHAKKLIVFLNE
 15 NNVPVQLTSISAPEHKFEGLTQIFQKAYEHEQHISESINNIVDHAIKGKDHATFNFLQWYVAEQ
 HEEEVLFKDILDKIELIGNENHGLYLADQYVKGIKSRKS
 (SEQ ID NO: 331)

20

The globular form of ferritin comprises 24 monomeric, subunit proteins, and has a capsid-like structure having 432 symmetry. Methods of constructing ferritin nanoparticles are known to the person of ordinary skill in the art and are further described herein (see, e.g., Zhang, Int. J. Mol. Sci., 12:5406-5421, 2011, which is incorporated herein by reference in its entirety).

25

For example, the ferritin polypeptide may be *E. coli* ferritin, *Helicobacter pylori* ferritin, human light chain ferritin, bullfrog ferritin or a hybrid thereof, such as *E. coli*-human hybrid ferritin, *E. coli*-bullfrog hybrid ferritin, or human-bullfrog hybrid ferritin. Exemplary amino acid sequences of ferritin polypeptides and nucleic acid sequences encoding ferritin polypeptides to be combined with the peptide according to the present invention or the protein according to the present invention can be found in GENBANK®, for example at
 30 accession numbers ZP 03085328, ZP 06990637, EJB64322.1, AAA35832, NP 000137 AAA49532, AAA49525, AAA49524 and AAA49523, which are specifically incorporated by reference herein in their entirety as available April 19, 2017. Preferably, the peptide according

to the present invention or the protein according to the present invention is linked to a ferritin protein including an amino acid sequence at least 80% (such as at least 85%, at least 90%, at least 95%, or at least 97%) identical to amino acid sequence set forth as SEQ ID NO: 331.

- 5 Preferably, the ferritin polypeptide is a *Helicobacter pylori* ferritin (such as a ferritin polypeptide set forth as SEQ ID NO: 331). More preferably, the ferritin polypeptide includes a substitution of the cysteine residue at position 31, such as a C31S, C31A or C31V substitution. The peptide according to the present invention or the protein according to the present invention can be linked to a *Helicobacter pylori* ferritin (such as a ferritin polypeptide
10 set forth as SEQ ID NO: 331) that preferably further includes a substitution of the cysteine residue at position 31 of the ferritin polypeptide, such as a C31S, C31A or C31V substitution.

- Preferably, the peptide according to the present invention or the protein according to the present invention may be linked to an encapsulin polypeptide to construct an encapsulin
15 nanoparticle. Accordingly, the protein nanoparticle comprising the peptide according to the present invention or the protein according to the present invention is preferably an encapsulin nanoparticle. Encapsulin proteins are a conserved family of bacterial proteins also known as linocin-like proteins that form large protein assemblies that function as a minimal compartment to package enzymes. The encapsulin assembly is made up of monomeric
20 subunits, which are polypeptides having a molecule weight of approximately 30 kDa. An example of the sequence of one such monomeric subunit is provided as SEQ ID NO: 332:

encapsulin polypeptide:

- MEFLKRSFAPLTEKQWQEIDNRAREIFKTQLYGRKFVDVEGPYGWEYAAHPLGEVEVLSDENE
25 VVKWGLRKSLPLIELRATFTLDLWELDNLERGKPNVDLSSLEETVRKVAEFEDEVIFRGCEKSGVK
GLLSFEERKIECGSTPKDLLEAIVRALSIFSKDGI EGPYTLVINTDRWINFLKEEAGHYPLEKRVEECL
RGGKIITTPRIEDALVVSERGGDFKLILGQDLSIGYEDREKDAVRLFITETFTFQVVNPEALILLKF
(SEQ ID NO: 332)

- 30 Following production, the monomeric subunits self-assemble into the globular encapsulin assembly including 60 monomeric subunits. Methods of constructing encapsulin nanoparticles are known to the person of ordinary skill in the art, and further described herein

(see, for example, Sutter et al., Nature Struct. and Mol. Biol., 15:939-947, 2008, which is incorporated by reference herein in its entirety). In specific examples, the encapsulin polypeptide is bacterial encapsulin, such as *E. coli* or *Thermotoga maritime* encapsulin.

- 5 An exemplary encapsulin sequence to be combined with the peptide according to the present invention or the protein according to the present invention is set forth as SEQ ID NO: 332.

Preferably, the peptide according to the present invention or the protein according to the present invention may be linked to a Sulfur Oxygenase Reductase (SOR) polypeptide to
10 construct a SOR nanoparticle. Accordingly, the protein nanoparticle comprising the peptide according to the present invention or the protein according to the present invention is preferably an SOR nanoparticle. SOR proteins are microbial proteins (for example from the thermoacidophilic archaeon *Acidianus ambivalens* that form 24 subunit protein assemblies. Methods of constructing SOR nanoparticles are known to the person of ordinary skill in the
15 art (see, e.g., Urich et al., Science, 311:996-1000, 2006, which is incorporated by reference herein in its entirety).

Furthermore, the peptide according to the present invention or the protein according to the present invention may also be linked to a Lumazine synthase polypeptide to construct a
20 Lumazine synthase nanoparticle. Accordingly, the protein nanoparticle comprising the peptide according to the present invention or the protein according to the present invention is preferably an Lumazine synthase nanoparticle.

Moreover, the peptide according to the present invention or the protein according to the present invention may also be linked to a pyruvate dehydrogenase polypeptide to construct
25 a pyruvate dehydrogenase nanoparticle. Accordingly, the protein nanoparticle comprising the peptide according to the present invention or the protein according to the present invention is preferably a pyruvate dehydrogenase nanoparticle.

30 Further preferred examples of protein nanoparticles, and methods for obtaining the same, are disclosed in Warangkana Lohcharoenkal, Liying Wang, Yi Charlie Chen, and Yon Rojanasakul, "Protein Nanoparticles as Drug Delivery Carriers for Cancer Therapy," BioMed

Research International, vol. 2014, Article ID 180549, 12 pages, 2014. doi:10.1155/2014/180549, which is incorporated herein by reference.

Preferably, the peptide according to the present invention or the protein according to the
5 present invention is linked to the N- or C-terminus of a nanoparticle protein, such as a ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase protein, for example with a linker, such as a GS-linker known in the art. Constructs are preferably made in HEK 293 cells, in particular since fusion proteins may be secreted from those cells and self-assemble into nanoparticles. The nanoparticles can be purified using known techniques, for example by a
10 few different chromatography procedures, e.g. Mono Q (anion exchange) followed by size exclusion (SUPEROSE® 6) chromatography.

The present invention also provides a fusion protein comprising (i) the peptide according to the present invention and (ii) a monomeric subunit of a nanoparticle protein, such as ferritin,
15 encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase protein, or any portion thereof which is capable of directing self-assembly of monomeric subunits into the globular form of the protein. Amino acid sequences from monomeric subunits of any known nanoparticle protein, such as ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase protein, can be used to produce fusion proteins with the peptide according to
20 the present invention or the protein according to the present invention, in particular so long as the monomeric subunit is capable of self-assembling into a nanoparticle displaying the the peptide according to the present invention on its surface.

The fusion proteins need not comprise the full-length sequence of a monomeric subunit
25 polypeptide of a nanoparticle protein, such as ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase protein. Portions, or regions, of the monomeric subunit polypeptide can be utilized so long as the portion comprises amino acid sequences that direct selfassembly of monomeric subunits into the globular form of the protein.

30 In some embodiments, it may be useful to engineer mutations into the amino acid sequence of the monomeric ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase

subunits. For example, it may be useful to alter sites such as enzyme recognition sites or glycosylation sites in order to give the fusion protein beneficial properties (e.g., half-life).

It will be understood by those skilled in the art that fusion of the peptide according to the present invention or the protein according to the present invention to the ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase protein should be done such that the portion of the fusion protein containing the peptide according to the present invention or the protein according to the present invention does not interfere with self-assembly of the monomeric ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase subunits into the globular protein, and that the ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase protein portion of the fusion protein does not interfere with the ability of the peptide according to the present invention or the protein according to the present invention to elicit an immune response.

In general, the nanoparticle protein and the peptide according to the present invention or the protein according to the present invention can be joined together directly without affecting the activity of either portion. Alternatively, the nanoparticle protein and the peptide according to the present invention or the protein according to the present invention are joined using a linker (also referred to as a spacer) sequence. For example, the ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase protein and the peptide according to the present invention or the protein according to the present invention can be joined together directly without affecting the activity of either portion. Alternatively, the ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase protein and the peptide according to the present invention or the protein according to the present invention are joined using a linker (also referred to as a spacer) sequence.

The linker sequence may be designed to position the ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase portion of the fusion protein and the portion of the fusion protein containing the peptide according to the present invention or the protein according to the present invention, with regard to one another, such that the fusion protein maintains the ability to assemble into nanoparticles, and also elicits an immune response to Plasmodium.

Preferably, the linker sequences comprise amino acids. Preferable amino acids to use are those having small side chains and/or those which are not charged. Such amino acids are less likely to interfere with proper folding and activity of the fusion protein. Accordingly, preferred amino acids to use in linker sequences, either alone or in combination are serine, glycine and alanine. One example of such a linker sequence is SGG. Amino acids can be added or subtracted as needed. Those skilled in the art are capable of determining appropriate linker sequences for construction of protein nanoparticles.

Preferably, the protein nanoparticles has a molecular weight of from 100 to 5000 kDa, such as approximately 500 to 4600 kDa. More preferably, a Ferritin nanoparticle has an approximate molecular weight of about 650 kDa, an Encapsulin nanoparticle has an approximate molecular weight of about 2100 kDa, a SOR nanoparticle has an approximate molecular weight of about 1000 kDa, a lumazine synthase nanoparticle has an approximate molecular weight of about 4000 kDa, and a pyruvate dehydrogenase nanoparticle has an approximate molecular weight of about 4600 kDa, when the protein nanoparticle includes the peptide according to the present invention or the protein according to the present invention.

The peptide according to the present invention or the protein according to the present invention linked to ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase proteins can self-assemble into multi-subunit protein nanoparticles, typically termed ferritin nanoparticles, encapsulin nanoparticles, SOR nanoparticles, lumazine synthase nanoparticles, and pyruvate dehydrogenase nanoparticles, respectively. The nanoparticles including the peptide according to the present invention or the protein according to the present invention have substantially the same structural characteristics as the native ferritin, encapsulin, SOR, lumazine synthase or pyruvate dehydrogenase nanoparticles that do not include the peptide according to the present invention or the protein according to the present invention. That is, they contain 24, 60, 24, 60, or 60 subunits (respectively) and have similar corresponding symmetry.

It is also preferred that the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, or the

protein nanoparticle according to the present invention specifically bind to the antibodies according to the present invention as described below, preferably with a K_d of 1 μ M or less.

As used herein, " K_d " refers to the dissociation constant for a given interaction, such as a polypeptide-ligand interaction or an antibody-antigen interaction. For example, for the bimolecular interaction of an antibody (such as the antibodies according to the present invention as described below) and an antigen (such as the peptide according to the present invention or the protein according to the present invention), it is the concentration of the individual components of the bimolecular interaction divided by the concentration of the complex. Methods of determining the K_d of an antibody: antigen interaction are familiar to the person of ordinary skill in the art.

Antibodies according to the present invention

Antibody binding to the peptide according to the invention

In a further aspect the present invention provides an antibody, or an antigen-binding fragment thereof, that (specifically) binds to a peptide according to the present invention. In other words, the antibody according to the present invention, or the antigen-binding fragment thereof, is able to recognize an epitope, in particular a CSP epitope, which corresponds to the peptide according to the present invention. Accordingly, the antibodies according to the present invention bind to a CSP epitope, which is located at the junction between the N-terminus of CSP and the NANP-repeat region, close to the functionally important region I of CSP.

Antibodies binding to that epitope, and thus to a peptide according to the present invention, were surprisingly found to greatly reduce liver parasite burden *in vivo*, indicating that such antibodies are able to potently inhibit (i) sporozoite invasion and (ii) liver stage parasite multiplication *in vivo*. Thereby, not only the disease in an individual can be prevented and/or treated, but also the spreading of the disease in a population can be inhibited.

Preferably, the antibody, or an antigen binding fragment thereof, according to the present invention is a human antibody. It is also preferred that the antibody, or an antigen binding fragment thereof, according to the present invention is a monoclonal antibody, preferably a human monoclonal antibody. Furthermore, it is also preferred that the antibody, or an antigen binding fragment thereof, according to the present invention is a recombinant antibody.

Preferably, the antibody according to the present invention, or an antigen binding fragment thereof, comprises an Fc moiety. More preferably, the Fc moiety is derived from human origin, e.g. from human IgG1, IgG2, IgG3, and/or IgG4, whereby human IgG1 is particularly preferred.

As used herein, the term "Fc moiety" refers to a sequence derived from the portion of an immunoglobulin heavy chain beginning in the hinge region just upstream of the papain cleavage site (e.g., residue 216 in native IgG, taking the first residue of heavy chain constant region to be 114) and ending at the C-terminus of the immunoglobulin heavy chain. Accordingly, an Fc moiety may be a complete Fc moiety or a portion (e.g., a domain) thereof. A complete Fc moiety comprises at least a hinge domain, a CH2 domain, and a CH3 domain (e.g., EU amino acid positions 216-446). An additional lysine residue (K) is sometimes present at the extreme C-terminus of the Fc moiety, but is often cleaved from a mature antibody. Each of the amino acid positions within an Fc moiety have been numbered according to the art-recognized EU numbering system of Kabat, see e.g., by Kabat et al., in "Sequences of Proteins of Immunological Interest", U.S. Dept. Health and Human Services, 1983 and 1987.

Preferably, in the context of the present invention an Fc moiety comprises at least one of: a hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant, portion, or fragment thereof. In preferred embodiments, an Fc moiety comprises at least a hinge domain, a CH2 domain or a CH3 domain. More preferably, the Fc moiety is a complete Fc moiety. The Fc moiety may also comprises one or more amino acid insertions, deletions, or substitutions relative to a naturally-occurring Fc moiety. For example, at least one of a hinge domain, CH2 domain or CH3 domain (or portion thereof) may be deleted. For example, an Fc moiety may comprise or consist of: (i) hinge domain (or portion thereof) fused to a CH2 domain (or portion thereof), (ii) a hinge domain (or portion thereof)

fused to a CH3 domain (or portion thereof), (iii) a CH2 domain (or portion thereof) fused to a CH3 domain (or portion thereof), (iv) a hinge domain (or portion thereof), (v) a CH2 domain (or portion thereof), or (vi) a CH3 domain or portion thereof.

5 It will be understood by one of ordinary skill in the art that the Fc moiety may be modified such that it varies in amino acid sequence from the complete Fc moiety of a naturally occurring immunoglobulin molecule, while retaining at least one desirable function conferred by the naturally-occurring Fc moiety. Such functions include Fc receptor (FcR) binding, antibody half-life modulation, ADCC function, protein A binding, protein G binding,
10 and complement binding. The portions of naturally occurring Fc moieties, which are responsible and/or essential for such functions are well known by those skilled in the art.

For example, to activate the complement cascade C1q binds to at least two molecules of IgG1 or one molecule of IgM, attached to the antigenic target (Ward, E. S., and Ghetie, V., *Ther. Immunol.* 2 (1995) 77-94). Burton, D. R., described (*Mol. Immunol.* 22 (1985) 161-206) that
15 the heavy chain region comprising amino acid residues 318 to 337 is involved in complement fixation. Duncan, A. R., and Winter, G. (*Nature* 332 (1988) 738-740), using site directed mutagenesis, reported that Glu318, Lys320 and Lys322 form the binding site to C1q. The role of Glu318, Lys320 and Lys 322 residues in the binding of C1q was confirmed by the ability
20 of a short synthetic peptide containing these residues to inhibit complement mediated lysis.

For example, FcR binding can be mediated by the interaction of the Fc moiety (of an antibody) with Fc receptors (FcRs), which are specialized cell surface receptors on hematopoietic cells. Fc receptors belong to the immunoglobulin superfamily, and were shown to mediate both the
25 removal of antibody-coated pathogens by phagocytosis of immune complexes, and the lysis of erythrocytes and various other cellular targets (e.g. tumor cells) coated with the corresponding antibody, via antibody dependent cell mediated cytotoxicity (ADCC; Van de Winkel, J. G., and Anderson, C. L., *J. Leukoc. Biol.* 49 (1991) 511-524). FcRs are defined by their specificity for immunoglobulin classes; Fc receptors for IgG antibodies are referred to as FcγR, for IgE as FcεR, for IgA as FcαR and so on and neonatal Fc receptors are referred to as FcRn. Fc receptor binding is described for example in Ravetch, J. V., and Kinet, J. P., *Annu. Rev. Immunol.* 9 (1991) 457-492; Capel, P. J., et al., *Immunomethods* 4 (1994) 25-34; de
30

Haas, M., et al., *J Lab. Clin. Med.* 126 (1995) 330-341; and Gessner, J. E., et al., *Ann. Hematol.* 76 (1998) 231-248.

Cross-linking of receptors by the Fc domain of native IgG antibodies (FcγR) triggers a wide variety of effector functions including phagocytosis, antibody-dependent cellular cytotoxicity, and release of inflammatory mediators, as well as immune complex clearance and regulation of antibody production. Therefore, Fc moieties providing cross-linking of receptors (FcγR) are preferred. In humans, three classes of FcγR have been characterized, which are: (i) FcγRI (CD64), which binds monomeric IgG with high affinity and is expressed on macrophages, monocytes, neutrophils and eosinophils; (ii) FcγRII (CD32), which binds complexed IgG with medium to low affinity, is widely expressed, in particular on leukocytes, is known to be a central player in antibody-mediated immunity, and which can be divided into FcγRIIA, FcγRIIB and FcγRIIC, which perform different functions in the immune system, but bind with similar low affinity to the IgG-Fc, and the ectodomains of these receptors are highly homologous; and (iii) FcγRIII (CD16), which binds IgG with medium to low affinity and exists as two types: FcγRIIIA found on NK cells, macrophages, eosinophils and some monocytes and T cells and mediating ADCC and FcγRIIIB, which is highly expressed on neutrophils. FcγRIIA is found on many cells involved in killing (e.g. macrophages, monocytes, neutrophils) and seems able to activate the killing process. FcγRIIB seems to play a role in inhibitory processes and is found on B-cells, macrophages and on mast cells and eosinophils. Importantly, 75% of all FcγRIIB is found in the liver (Ganesan, L. P. et al., 2012: FcγRIIb on liver sinusoidal endothelium clears small immune complexes. *Journal of Immunology* 189: 4981–4988). FcγRIIB is abundantly expressed on Liver Sinusoidal Endothelium, called LSEC, and in Kupffer cells in the liver and LSEC are the major site of small immune complexes clearance (Ganesan, L. P. et al., 2012: FcγRIIb on liver sinusoidal endothelium clears small immune complexes. *Journal of Immunology* 189: 4981–4988).

Accordingly, in the present invention such antibodies, and antigen binding fragments thereof, are preferred, which are able to bind to FcγRIIb, for example antibodies comprising an Fc moiety for binding to FcγRIIb, in particular an Fc region, such as, for example IgG-type antibodies. Moreover, it is possible to engineer the Fc moiety to enhance FcγRIIB binding by

introducing the mutations S267E and L328F as described by Chu, S. Y. et al., 2008: Inhibition of B cell receptor-mediated activation of primary human B cells by coengagement of CD19 and FcγRIIb with Fc-engineered antibodies. *Molecular Immunology* 45, 3926–3933. Thereby, the clearance of immune complexes can be enhanced (Chu, S., et al., 2014: Accelerated Clearance of IgE In Chimpanzees Is Mediated By Xmab7195, An Fc-Engineered Antibody With Enhanced Affinity For Inhibitory Receptor FcγRIIb. *Am J Respir Crit, American Thoracic Society International Conference Abstracts*). Accordingly, in the context of the present invention such antibodies, or antigen binding fragments thereof, are preferred, which comprise an engineered Fc moiety with the mutations S267E and L328F, in particular as described by Chu, S. Y. et al., 2008: Inhibition of B cell receptor-mediated activation of primary human B cells by coengagement of CD19 and FcγRIIb with Fc-engineered antibodies. *Molecular Immunology* 45, 3926–3933.

On B-cells it seems to function to suppress further immunoglobulin production and isotype switching to say for example the IgE class. On macrophages, FcγRIIB acts to inhibit phagocytosis as mediated through FcγRIIA. On eosinophils and mast cells the b form may help to suppress activation of these cells through IgE binding to its separate receptor.

Regarding FcγRI binding, modification in native IgG of at least one of E233-G236, P238, D265, N297, A327 and P329 reduces binding to FcγRI. IgG2 residues at positions 233-236, substituted into IgG1 and IgG4, reduces binding to FcγRI by 10³-fold and eliminated the human monocyte response to antibody-sensitized red blood cells (Armour, K. L., et al. *Eur. J. Immunol.* 29 (1999) 2613-2624). Regarding FcγRII binding, reduced binding for FcγRIIA is found e.g. for IgG mutation of at least one of E233-G236, P238, D265, N297, A327, P329, D270, Q295, A327, R292 and K414. Regarding FcγRIII binding, reduced binding to FcγRIIIA is found e.g. for mutation of at least one of E233-G236, P238, D265, N297, A327, P329, D270, Q295, A327, S239, E269, E293, Y296, V303, A327, K338 and D376. Mapping of the binding sites on human IgG1 for Fc receptors, the above mentioned mutation sites and methods for measuring binding to FcγRI and FcγRIIA are described in Shields, R. L., et al., *J. Biol. Chem.* 276 (2001) 6591-6604.

Regarding binding to the crucial FcγRII, two regions of native IgG Fc appear to be critical for interactions of FcγRIIs and IgGs, namely (i) the lower hinge site of IgG Fc, in particular amino acid residues L, L, G, G (234 – 237, EU numbering), and (ii) the adjacent region of the CH2 domain of IgG Fc, in particular a loop and strands in the upper CH2 domain adjacent to the lower hinge region, e.g. in a region of P331 (Wines, B.D., et al., J. Immunol. 2000; 164: 5313 – 5318). Moreover, FcγRI appears to bind to the same site on IgG Fc, whereas FcRn and Protein A bind to a different site on IgG Fc, which appears to be at the CH2-CH3 interface (Wines, B.D., et al., J. Immunol. 2000; 164: 5313 – 5318).

For example, the Fc moiety may comprise or consist of at least the portion of an Fc moiety that is known in the art to be required for FcRn binding or extended half-life. Alternatively or additionally, the Fc moiety of the antibody of the invention comprises at least the portion of known in the art to be required for Protein A binding and/or the Fc moiety of the antibody of the invention comprises at least the portion of an Fc molecule known in the art to be required for protein G binding. A preferred Fc moiety comprises at least the portion known in the art to be required for FcγR binding. As outlined above, a preferred Fc moiety may thus at least comprise (i) the lower hinge site of native IgG Fc, in particular amino acid residues L, L, G, G (234 – 237, EU numbering), and (ii) the adjacent region of the CH2 domain of native IgG Fc, in particular a loop and strands in the upper CH2 domain adjacent to the lower hinge region, e.g. in a region of P331, for example a region of at least 3, 4, 5, 6, 7, 8, 9, or 10 consecutive amino acids in the upper CH2 domain of native IgG Fc around P331, e.g. between amino acids 320 and 340 (EU numbering) of native IgG Fc.

Preferably, the antibody, or antigen binding fragment thereof, according to the present invention comprises an Fc region. As used herein, the term “Fc region” refers to the portion of an immunoglobulin formed by two or more Fc moieties of antibody heavy chains. For example, the Fc region may be monomeric or “single-chain” Fc region (i.e., a scFc region). Single chain Fc regions are comprised of Fc moieties linked within a single polypeptide chain (e.g., encoded in a single contiguous nucleic acid sequence). Exemplary scFc regions are disclosed in WO 2008/143954 A2. Preferably, the Fc region is a dimeric Fc region. A “dimeric Fc region” or “dcFc” refers to the dimer formed by the Fc moieties of two separate immunoglobulin heavy chains. The dimeric Fc region may be a homodimer of two identical

Fc moieties (e.g., an Fc region of a naturally occurring immunoglobulin) or a heterodimer of two non-identical Fc moieties.

The Fc moieties of the Fc region may be of the same or different class and/or subclass. For example, the Fc moieties may be derived from an immunoglobulin (e.g., a human immunoglobulin) of an IgG1, IgG2, IgG3 or IgG4 subclass. Preferably, the Fc moieties of Fc region are of the same class and subclass. However, the Fc region (or one or more Fc moieties of an Fc region) may also be chimeric, whereby a chimeric Fc region may comprise Fc moieties derived from different immunoglobulin classes and/or subclasses. For example, at least two of the Fc moieties of a dimeric or single-chain Fc region may be from different immunoglobulin classes and/or subclasses. Additionally or alternatively, the chimeric Fc regions may comprise one or more chimeric Fc moieties. For example, the chimeric Fc region or moiety may comprise one or more portions derived from an immunoglobulin of a first subclass (e.g., an IgG1, IgG2, or IgG3 subclass) while the remainder of the Fc region or moiety is of a different subclass. For example, an Fc region or moiety of an Fc polypeptide may comprise a CH2 and/or CH3 domain derived from an immunoglobulin of a first subclass (e.g., an IgG1, IgG2 or IgG4 subclass) and a hinge region from an immunoglobulin of a second subclass (e.g., an IgG3 subclass). For example, the Fc region or moiety may comprise a hinge and/or CH2 domain derived from an immunoglobulin of a first subclass (e.g., an IgG4 subclass) and a CH3 domain from an immunoglobulin of a second subclass (e.g., an IgG1, IgG2, or IgG3 subclass). For example, the chimeric Fc region may comprise an Fc moiety (e.g., a complete Fc moiety) from an immunoglobulin for a first subclass (e.g., an IgG4 subclass) and an Fc moiety from an immunoglobulin of a second subclass (e.g., an IgG1, IgG2 or IgG3 subclass). For example, the Fc region or moiety may comprise a CH2 domain from an IgG4 immunoglobulin and a CH3 domain from an IgG1 immunoglobulin. For example, the Fc region or moiety may comprise a CH1 domain and a CH2 domain from an IgG4 molecule and a CH3 domain from an IgG1 molecule. For example, the Fc region or moiety may comprise a portion of a CH2 domain from a particular subclass of antibody, e.g., EU positions 292-340 of a CH2 domain. For example, an Fc region or moiety may comprise amino acids a positions 292-340 of CH2 derived from an IgG4 moiety and the remainder of CH2 derived from an IgG1 moiety (alternatively, 292-340 of CH2 may be derived from an IgG1 moiety and the remainder of CH2 derived from an IgG4 moiety).

Moreover, an Fc region or moiety may (additionally or alternatively) for example comprise a chimeric hinge region. For example, the chimeric hinge may be derived, e.g. in part, from an IgG1, IgG2, or IgG4 molecule (e.g., an upper and lower middle hinge sequence) and, in part, from an IgG3 molecule (e.g., an middle hinge sequence). In another example, an Fc region or moiety may comprise a chimeric hinge derived, in part, from an IgG1 molecule and, in part, from an IgG4 molecule. In another example, the chimeric hinge may comprise upper and lower hinge domains from an IgG4 molecule and a middle hinge domain from an IgG1 molecule. Such a chimeric hinge may be made, for example, by introducing a proline substitution (Ser228Pro) at EU position 228 in the middle hinge domain of an IgG4 hinge region. In another embodiment, the chimeric hinge can comprise amino acids at EU positions 233-236 are from an IgG2 antibody and/or the Ser228Pro mutation, wherein the remaining amino acids of the hinge are from an IgG4 antibody (e.g., a chimeric hinge of the sequence ESKYGPPCPPCPAPPVAGP). Further chimeric hinges, which may be used in the Fc moiety of the antibody according to the present invention are described in US 2005/0163783 A1.

In the present invention it is preferred that the Fc moiety, or the Fc region, comprises or consists of an amino acid sequence derived from a human immunoglobulin sequence (e.g., from an Fc region or Fc moiety from a human IgG molecule). However, polypeptides may comprise one or more amino acids from another mammalian species. For example, a primate Fc moiety or a primate binding site may be included in the subject polypeptides. Alternatively, one or more murine amino acids may be present in the Fc moiety or in the Fc region.

Preferably, the antibody according to the present invention comprises, in particular in addition to an Fc moiety as described above, other parts derived from a constant region, in particular from a constant region of IgG, preferably from a constant region of IgG1, more preferably from a constant region of human IgG1. More preferably, the antibody according to the present invention comprises, in particular in addition to an Fc moiety as described above, all other parts of the constant regions, in particular all other parts of the constant regions of IgG, preferably all other parts of the constant regions of IgG1, more preferably all other parts of the constant regions of human IgG1.

Particularly preferred sequences of constant regions are the amino acid sequences according to SEQ ID NOs: 313 – 315 (nucleic acid sequences according to SEQ ID NOs: 316 – 318). Preferably, the amino acid sequence of IgG1 CH1-CH2-CH3 is according to SEQ ID NO: 313 or a functional sequence variant thereof, as described herein.

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As outlined above, a particularly preferred antibody according to the present invention comprises a (complete) Fc region derived from human IgG1. More preferably, the antibody according to the present invention comprises, in particular in addition to a (complete) Fc region derived from human IgG1 also all other parts of the constant regions of IgG, preferably all other parts of the constant regions of IgG1, more preferably all other parts of the constant regions of human IgG1.

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Preferably, the antibody according to the present invention comprises a (complete) Fc moiety/Fc region, wherein the interaction/binding with FcR is not compromised. In general, binding of the antibody to an Fc receptor may be assessed by various methods known to the skilled person, such as ELISA (Hessell AJ, Hangartner L, Hunter M, Havenith CEG, Beurskens FJ, Bakker JM, Lanigan CMS, Landucci G, Forthal DN, Parren PWHL, et al.: Fc receptor but not complement binding is important in antibody protection against HIV. *Nature* 2007, 449:101–104; Grevys A, Bern M, Foss S, Bratlie DB, Moen A, Gunnarsen KS, Aase A, Michaelsen TE, Sandlie I, Andersen JT: Fc Engineering of Human IgG1 for Altered Binding to the Neonatal Fc Receptor Affects Fc Effector Functions. 2015, 194:5497–5508) or flow-cytometry (Perez LG, Costa MR, Todd CA, Haynes BF, Montefiori DC: Utilization of immunoglobulin G Fc receptors by human immunodeficiency virus type 1: a specific role for antibodies against the membrane-proximal external region of gp41. *J Virol* 2009, 83:7397–7410; Piccoli L, Campo I, Fregni CS, Rodriguez BMF, Minola A, Sallusto F, Luisetti M, Corti D, Lanzavecchia A: Neutralization and clearance of GM-CSF by autoantibodies in pulmonary alveolar proteinosis. *Nat Commun* 2015, 6:1–9).

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In general, the antibody according to the present invention may be glycosylated. N-linked glycans attached to the CH2 domain of a heavy chain, for instance, can influence C1q and FcR binding, with glycosylated antibodies having lower affinity for these receptors. Accordingly, the CH2 domain of the Fc moiety of the antibody according to the present

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invention may comprise one or more mutations, in which a glycosylated residue is substituted by a non-glycosylated residue. The glycan structure can also affect activity e.g. differences in complement-mediated cell death may be seen depending on the number of galactose sugars (0, 1 or 2) at the terminus of a glycan's biantennary chain. Preferably, the antibody's glycans do not lead to a human immunogenic response after administration.

Furthermore, the antibody according to the present invention can be modified by introducing random amino acid mutations into particular region of the CH2 or CH3 domain of the heavy chain in order to alter their binding affinity for FcR and/or their serum half-life in comparison to unmodified antibodies. Examples of such modifications include, but are not limited to, substitutions of at least one amino acid from the heavy chain constant region selected from the group consisting of amino acid residues 250, 314, and 428.

Preferably, the antibody, or an antigen-binding fragment thereof, according to the present invention comprises a variable region of the heavy chain of the antibody, or of the antigen-binding fragment thereof, (VH), which is encoded by a nucleic acid comprising a gene (segment) of the VH3 gene family, preferably the gene (segment) VH3-30.

In general, the antibody according to the present invention, or the antigen binding fragment thereof, preferably comprises (at least) three complementarity determining regions (CDRs) on a heavy chain and (at least) three CDRs on a light chain. In general, complementarity determining regions (CDRs) are the hypervariable regions present in heavy chain variable domains and light chain variable domains. Typically, the CDRs of a heavy chain and the connected light chain of an antibody together form the antigen receptor. Usually, the three CDRs (CDR1, CDR2, and CDR3) are arranged non-consecutively in the variable domain. Since antigen receptors are typically composed of two variable domains (on two different polypeptide chains, i.e. heavy and light chain), there are six CDRs for each antigen receptor (heavy chain: CDRH1, CDRH2, and CDRH3; light chain: CDRL1, CDRL2, and CDRL3). A single antibody molecule usually has two antigen receptors and therefore contains twelve CDRs. The CDRs on the heavy and/or light chain may be separated by framework regions, whereby a framework region (FR) is a region in the variable domain which is less "variable"

than the CDR. For example, a chain (or each chain, respectively) may be composed of four framework regions, separated by three CDR's.

The sequences of the heavy chains and light chains of exemplary antibodies of the invention, comprising three different CDRs on the heavy chain and three different CDRs on the light chain were determined. The position of the CDR amino acids are defined according to the IMGT numbering system (IMGT: <http://www.imgt.org/>; cf. Lefranc, M.-P. et al. (2009) *Nucleic Acids Res.* 37, D1006-D1012).

- 10 Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs:
- 15 66, 84, 138, 156, 208, 226, 260, 278 and 296, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.
- 20 More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of
- 25 SEQ ID NOs: 66, 84, 138, 208, 226 and 278, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.
- Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one
- 30 CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to SEQ ID

NO: 66 or according to SEQ ID NO: 226; or of a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Still more preferably, the antibody, or the antigen binding fragment thereof, according to the

5 present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to SEQ ID

10 NO: 208 or according to SEQ ID NO: 278; or of a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one

15 CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to SEQ ID

NO: 84 or according to SEQ ID NO: 138; or of a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

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Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

25 (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to any of SEQ ID NOs: 64, 82, 136, 154, 206, 224, 258, 276, and 294, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;

30 (ii) the at least one CDRH2 comprises an amino acid sequence according to any of SEQ ID NOs: 65, 83, 137, 155, 207, 225, 259, 277, and 295, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least

88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or

- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to any of SEQ ID NOs: 66, 84, 138, 156, 208, 226, 260, 278 and 296, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to any of SEQ ID NOs: 64, 82, 136, 206, 224, and 276, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- (ii) the at least one CDRH2 comprises an amino acid sequence according to any of SEQ ID NOs: 65, 83, 137, 207, 225, and 277, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to any of SEQ ID NOs: 66, 84, 138, 208, 226, and 278, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to SEQ ID NO: 64 or according to SEQ ID NO: 224; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- (ii) the at least one CDRH2 comprises an amino acid sequence according to SEQ ID NO: 65 or according to SEQ ID NO: 225; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to SEQ ID NO: 66 or according to SEQ ID NO: 226; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to SEQ ID NO: 206 or according to SEQ ID NO: 276; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- (ii) the at least one CDRH2 comprises an amino acid sequence according to SEQ ID NO: 207 or according to SEQ ID NO: 277; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to SEQ ID NO: 208 or according to SEQ ID NO: 278; or a functional sequence variant

thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

- 5 Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein
- 10 (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to SEQ ID NO: 82 or according to SEQ ID NO: 136; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- 15 (ii) the at least one CDRH2 comprises an amino acid sequence according to SEQ ID NO: 83 or according to SEQ ID NO: 137; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- 20 (iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to SEQ ID NO: 84 or according to SEQ ID NO: 138; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.
- 25 It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein
- 30 (i) the at least one CDRL1 comprises an amino acid sequence according to any of SEQ ID NOs: 67, 85, 139, 157, 209, 227, 261, 279, and 297, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least

88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;

(ii) the at least one CDRL2 comprises an amino acid sequence according to any of SEQ ID NOs: 68, 69, 86, 87, 140, 141, 158, 159, 210, 211, 228, 229, 262, 263, 280, 281, 298 and 299, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or

(iii) the at least one CDRL3 amino comprises an amino acid sequence according to any of SEQ ID NOs: 70, 88, 142, 160, 212, 230, 264, 282, and 300 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

(i) the at least one CDRL1 comprises an amino acid sequence according to any of SEQ ID NOs: 67, 85, 139, 209, 227, and 279; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;

(ii) the at least one CDRL2 comprises an amino acid sequence according to any of SEQ ID NOs: 68, 69, 86, 87, 140, 141, 210, 211, 228, 229, 280, and 281; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or

(iii) the at least one CDRL3 amino comprises an amino acid sequence according to any of SEQ ID NOs: 70, 88, 142, 212, 230, and 282; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 67; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- 10 (ii) the at least one CDRL2 comprises an amino acid sequence according to SEQ ID NO: 68 or 69; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- 15 (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 70; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 209; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- 25 (ii) the at least one CDRL2 comprises an amino acid sequence according to SEQ ID NO: 210 or 211; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- 30 (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 212; or a functional sequence variant thereof having at least 70%, at least

75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 227; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- (ii) the at least one CDRL2 comprises an amino acid sequence according to SEQ ID NO: 228 or 229; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 230; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 279; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- (ii) the at least one CDRL2 comprises an amino acid sequence according to SEQ ID NO: 280 or 281; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- (iii) the at least one CDRL3 amino comprises an amino acid according to SEQ ID NO: 282; or a functional sequence variant thereof having at least 70%, at least 75%, at

least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Particularly preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 139; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- (ii) the at least one CDRL2 comprises an amino acid sequence according to SEQ ID NO: 140 or 141; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 142; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one CDRL1 comprises an amino acid sequence according to SEQ ID NO: 85; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- (ii) the at least one CDRL2 comprises an amino acid sequence according to SEQ ID NO: 86 or 87; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or
- (iii) the at least one CDRL3 amino comprises an amino acid sequence according to SEQ ID NO: 88; or a functional sequence variant thereof having at least 70%, at least 75%,

at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences (i) according to SEQ ID NOs: 64 - 66; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 82 - 84; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iii) according to SEQ ID NOs: 136 - 138; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) according to SEQ ID NOs: 154 - 156; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (v) according to SEQ ID NOs: 206 - 208; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) according to SEQ ID NOs: 224 - 226; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vii) according to SEQ ID NOs: 258 - 260; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (viii) according to SEQ ID NOs: 276 - 278; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ix) according to SEQ ID NOs: 294 - 296; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 64 – 68
5 and 70; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 64 – 67 and 69 – 70; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least
10 96%, at least 97%, at least 98% or at least 99% sequence identity; (iii) according to SEQ ID NOs: 82 – 86 and 88; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) according to SEQ ID NOs: 82 – 85 and 87 – 88; or functional sequence variants thereof having at least 70%, at
15 least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (v) according to SEQ ID NOs: 136 – 140 and 142; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) according
20 to SEQ ID NOs: 136 – 139 and 141 – 142; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vii) according to SEQ ID NOs: 154 – 158 and 160; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least
25 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (viii) according to SEQ ID NOs: 154 – 157 and 159 – 160; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ix) according to SEQ ID NOs: 206 – 210 and 212; or functional sequence
30 variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (x) according to SEQ ID NOs: 206 – 209 and 211 – 212; or functional

sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xi) according to SEQ ID NOs: 224 – 228 and 230; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xii) according to SEQ ID NOs: 224 - 227 and 229 – 230; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xiii) according to SEQ ID NOs: 258 – 262 and 264; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xiv) according to SEQ ID NOs: 258 – 261 and 263 – 264; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xv) according to SEQ ID NOs: 276 – 280 and 282; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xvi) according to SEQ ID NOs: 276 – 279 and 281 – 282; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xvii) according to SEQ ID NOs: 294 – 298 and 300; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xviii) according to SEQ ID NOs: 294 – 297 and 299 – 300; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 64 – 68

and 70, respectively; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 64 – 67 and 69 – 70; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 224 – 228 and 230; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 224 - 227 and 229 – 230; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 276 – 280 and 282; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 276 – 279 and 281 – 282; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 206 – 210 and 212; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at

least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 206 – 209 and 211 – 212; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

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Particularly preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 136 – 140 and 142; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 136 – 139 and 141 – 142; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

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Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 82 – 86 and 88; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 82 – 85 and 87 – 88; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

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In addition, it is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) and, optionally, a light chain variable region (VL), wherein the heavy chain variable region (VH) comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 71, 89, 143, 161, 213, 231, 265, 283, and 301; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

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Moreover, it is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises (i) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 71 or a functional sequence variant thereof having
5 at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 72 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%,
10 at least 98% or at least 99% sequence identity; (ii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 89 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 90
15 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 143 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least
20 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 144 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) a heavy chain variable region (VH) amino
25 acid sequence according to SEQ ID NO: 161 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 162 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at
30 least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (v) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 213 or a functional sequence variant thereof

having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 214 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 231 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 232 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 265 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 266 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (viii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 283 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 284 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (ix) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 301 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 302 or a functional sequence variant thereof having at least 70%,

at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 71 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 72 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 231 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 232 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 283 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 284 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 213 or a functional sequence variant thereof having at least 70%,
5 at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 214 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at
10 least 99% sequence identity.

Particularly preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 143 or a functional sequence variant thereof having at least 70%,
15 at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 144 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at
20 least 99% sequence identity.

Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 89 or a functional sequence variant thereof having at least 70%, at
25 least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 90 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at
30 least 99% sequence identity.

Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention is gMGG3, gMGG4, gMGH2, gMGH3, gMGU5, gMGU8, gMGU11, gMGU12 or gMGV3, preferably the antibody, or the antigen binding fragment thereof, is gMGG3, gMGG4, gMGH2, gMGU5, gMGU8 or gMGU12, more preferably the antibody, or the antigen binding fragment thereof, is gMGG4 or gMGH2.

The present inventors have isolated monoclonal antibody (mAb) according to the present invention, which are referred to herein as MGG3, MGG4, MGH2, MGH3, MGU5, MGU8, MGU11, MGU12 and MGV3 (cf. Tables 1 and 2, Example 1). Based on those antibodies, in particular on the VH and VL genes of those antibodies, the terms "gMGG3", "gMGG4", "gMGH2", "gMGH3", "gMGU5", "gMGU8", "gMGU11", "gMGU12", and "gMGV3", as used herein, refer to the respective "generic" antibodies, or antigen binding fragments thereof.

Namely, "gMGG3" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 64, a CDRH2 amino acid sequence according to SEQ ID NO: 65, a CDRH3 amino acid sequence according to SEQ ID NO: 66, a CDRL1 amino acid sequence according to SEQ ID NO: 67, a CDRL2 amino acid sequence according to SEQ ID NO: 68 or 69, and a CDRL3 amino acid sequence according to SEQ ID NO: 70. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 71 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 72.

"gMGG4" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 82, a CDRH2 amino acid sequence according to SEQ ID NO: 83, a CDRH3 amino acid sequence according to SEQ ID NO: 84, a CDRL1 amino acid sequence according to SEQ ID NO: 85, a CDRL2 amino acid sequence according to SEQ ID NO: 86 or 87, and a CDRL3 amino acid sequence according to SEQ ID NO: 88. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 89 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 90.

“gMGH2” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 136, a CDRH2 amino acid sequence according to SEQ ID NO: 137, a CDRH3 amino acid sequence according to SEQ ID NO: 138, a CDRL1 amino acid sequence according to SEQ ID NO: 139, a CDRL2 amino acid sequence according to SEQ ID NO: 140 or 141, and a CDRL3 amino acid sequence according to SEQ ID NO: 142. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 143 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 144.

“gMGH3” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 154, a CDRH2 amino acid sequence according to SEQ ID NO: 155, a CDRH3 amino acid sequence according to SEQ ID NO: 156, a CDRL1 amino acid sequence according to SEQ ID NO: 157, a CDRL2 amino acid sequence according to SEQ ID NO: 158 or 159, and a CDRL3 amino acid sequence according to SEQ ID NO: 160. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 161 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 162.

“gMGU5” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 206, a CDRH2 amino acid sequence according to SEQ ID NO: 207, a CDRH3 amino acid sequence according to SEQ ID NO: 208, a CDRL1 amino acid sequence according to SEQ ID NO: 209, a CDRL2 amino acid sequence according to SEQ ID NO: 210 or 211, and a CDRL3 amino acid sequence according to SEQ ID NO: 212. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 213 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 214.

“gMGU8” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 224, a CDRH2 amino acid sequence according to SEQ ID NO: 225, a CDRH3 amino acid sequence according to SEQ ID NO: 226, a CDRL1 amino acid sequence according to SEQ ID NO: 227, a CDRL2 amino acid sequence according to SEQ ID NO: 228 or 229, and a CDRL3 amino acid sequence according to SEQ

ID NO: 230. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 231 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 232.

5 "gMGU11" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 258, a CDRH2 amino acid sequence according to SEQ ID NO: 259, a CDRH3 amino acid sequence according to SEQ ID NO: 260, a CDRL1 amino acid sequence according to SEQ ID NO: 261, a CDRL2 amino acid sequence according to SEQ ID NO: 262 or 263, and a CDRL3 amino acid sequence
10 according to SEQ ID NO: 264. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 265 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 266.

"gMGU12" refers to an antibody, or antigen binding fragment thereof, having a CDRH1
15 amino acid sequence according to SEQ ID NO: 276, a CDRH2 amino acid sequence according to SEQ ID NO: 277, a CDRH3 amino acid sequence according to SEQ ID NO: 278, a CDRL1 amino acid sequence according to SEQ ID NO: 279, a CDRL2 amino acid sequence according to SEQ ID NO: 280 or 281, and a CDRL3 amino acid sequence according to SEQ ID NO: 282. The heavy chain variable region (V_H) has preferably an amino
20 acid sequence according to SEQ ID NO: 283 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 284.

"gMGV3" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 294, a CDRH2 amino acid sequence according to
25 SEQ ID NO: 295, a CDRH3 amino acid sequence according to SEQ ID NO: 296, a CDRL1 amino acid sequence according to SEQ ID NO: 297, a CDRL2 amino acid sequence according to SEQ ID NO: 298 or 299, and a CDRL3 amino acid sequence according to SEQ ID NO: 300. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 301 and the light chain variable region (V_L) has preferably an amino
30 acid sequence according to SEQ ID NO: 302.

Antibody binding to P. falciparum sporozoites

In a further aspect the present invention provides an antibody, or an antigen-binding fragment thereof, that (specifically) binds to *P. falciparum* sporozoites. More preferably, the antibody according to the present invention, or the antigen-binding fragment thereof, (specifically) binds to *Plasmodium* circumsporozoite protein, most preferably to *Plasmodium* circumsporozoite protein according to SEQ ID NO: 24. In other words, the antibody according to the present invention, or the antigen-binding fragment thereof, is able to recognize an epitope, in particular a CSP epitope.

Preferably, the antibody, or an antigen binding fragment thereof, according to the present invention is a human antibody. It is also preferred that the antibody, or an antigen binding fragment thereof, according to the present invention is a monoclonal antibody, preferably a human monoclonal antibody. Furthermore, it is also preferred that the antibody, or an antigen binding fragment thereof, according to the present invention is a recombinant antibody.

Preferably, the antibody according to the present invention, or an antigen binding fragment thereof, comprises an Fc moiety as described above. It is understood that preferred embodiments of the Fc moiety of the antibody according to the present invention binding to the peptide according to the present invention correspond to preferred embodiments of the Fc moiety of the antibody according to the present invention binding to *P. falciparum* sporozoites. For example, the Fc moiety is preferably derived from human origin, e.g. from human IgG1, IgG2, IgG3, and/or IgG4, whereby human IgG1 is particularly preferred.

For all antibodies according to the present invention, i.e. antibodies binding to the peptide according to the present invention and antibodies binding to *P. falciparum* sporozoites, it is also preferred that the antibody, or an antigen binding fragment thereof, does not comprise an Fc moiety. In particular it is preferred that the antibody according to the present invention, or an antigen binding fragment thereof, is a purified antibody, a single chain antibody, Fab, Fab', F(ab')₂, Fv or scFv.

As described above, the antibody according to the present invention, or the antigen binding fragment thereof, preferably comprises (at least) three complementarity determining regions (CDRs) on a heavy chain and (at least) three CDRs on a light chain. In general, complementarity determining regions (CDRs) are the hypervariable regions present in heavy chain variable domains and light chain variable domains. Typically, the CDRs of a heavy chain and the connected light chain of an antibody together form the antigen receptor. Usually, the three CDRs (CDR1, CDR2, and CDR3) are arranged non-consecutively in the variable domain. Since antigen receptors are typically composed of two variable domains (on two different polypeptide chains, i.e. heavy and light chain), there are six CDRs for each antigen receptor (heavy chain: CDRH1, CDRH2, and CDRH3; light chain: CDRL1, CDRL2, and CDRL3). A single antibody molecule usually has two antigen receptors and therefore contains twelve CDRs. The CDRs on the heavy and/or light chain may be separated by framework regions, whereby a framework region (FR) is a region in the variable domain which is less "variable" than the CDR. For example, a chain (or each chain, respectively) may be composed of four framework regions, separated by three CDR's.

The sequences of the heavy chains and light chains of exemplary antibodies of the invention, comprising three different CDRs on the heavy chain and three different CDRs on the light chain were determined. The position of the CDR amino acids are defined according to the IMGT numbering system (IMGT: <http://www.imgt.org/>; cf. Lefranc, M.-P. et al. (2009) Nucleic Acids Res. 37, D1006-D1012).

Table 1 below shows the SEQ ID NOs of the amino acid sequences of the heavy chain CDR's (CDRH1, CDRH2, and CDRH3) and of the heavy chain variable region (referred to as "VH") of exemplary antibodies according to the present invention:

Antibody name	CDRH1	CDRH2	CDRH3	VH
MGG1	28	29	30	35
MGG2	46	47	48	53
MGG3	64	65	66	71
MGG4	82	83	84	89

Antibody name	CDRH1	CDRH2	CDRH3	VH
MGG8	100	101	102	107
MGH1	118	119	120	125
MGH2	136	137	138	143
MGH3	154	155	156	161
MGU1	172	173	174	178
MGU3	188	189	190	195
MGU5	206	207	208	213
MGU8	224	225	226	231
MGU10	242	243	244	248
MGU11	258	259	260	265
MGU12	276	277	278	283
MGV3	294	295	296	301

Table 1.

Table 2 below shows the SEQ ID NOs of the amino acid sequences of the light chain CDR's (CDRL1, CDRL2, and CDRL3) and of the light chain variable region (referred to as "VL") of

5 exemplary antibodies according to the present invention:

Antibody name	CDRL1	CDRL2	CDRL2 long	CDRL3	VL
MGG1	31	32	33	34	36
MGG2	49	50	51	52	54
MGG3	67	68	69	70	72
MGG4	85	86	87	88	90
MGG8	103	104	105	106	108
MGH1	121	122	123	124	126
MGH2	139	140	141	142	144
MGH3	157	158	159	160	162
MGU1	175	176	—	177	179
MGU3	191	192	193	194	196

MGU5	209	210	211	212	214
MGU8	227	228	229	230	232
MGU10	245	246	—	247	249
MGU11	261	262	263	264	266
MGU12	279	280	281	282	284
MGV3	297	298	299	300	302

Table 2.

It is thus preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises amino acid sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity to at least one of the CDR sequences, the VH sequence and/or the VL sequence shown in Table 1 and/or in Table 2.

Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein at least one CDR, preferably the at least one heavy chain CDRH3, comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 30, 48, 66, 84, 102, 120, 138, 156, 174, 190, 208, 226, 260, 244, 278 and 296, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

- (i) the at least one heavy chain CDRH1 comprises an amino acid sequence according to any of SEQ ID NOs: 28, 46, 64, 82, 100, 118, 136, 154, 172, 188, 206, 224, 242, 258, 276, and 294, or a functional sequence variant thereof having at least 70%, at

least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;

(ii) the at least one CDRH2 comprises an amino acid sequence according to any of SEQ ID NOs: 29, 47, 65, 83, 101, 119, 137, 155, 173, 189, 207, 225, 243, 259, 277, and 295, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or

(iii) the at least one heavy chain CDRH3 comprises an amino acid sequence according to any of SEQ ID NOs: 30, 48, 66, 84, 102, 120, 138, 156, 174, 190, 208, 226, 260, 244, 278 and 296, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

It is also preferred that the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain comprising at least one CDRH1, at least one CDRH2 and at least one CDRH3 and a light chain comprising at least one CDRL1, at least one CDRL2 and at least one CDRL3, wherein

(i) the at least one CDRL1 comprises an amino acid sequence according to any of SEQ ID NOs: 31, 49, 67, 85, 103, 121, 139, 157, 175, 191, 209, 227, 245, 261, 279, and 297, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;

(ii) the at least one CDRL2 comprises an amino acid sequence according to any of SEQ ID NOs: 32, 33, 50, 51, 68, 69, 86, 87, 104, 105, 122, 123, 140, 141, 158, 159, 176, 192, 193, 210, 211, 228, 229, 246, 262, 263, 280, 281, 298 and 299, or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and/or

(iii) the at least one CDRL3 amino comprises an amino acid sequence according to any of SEQ ID NOs: 34, 52, 70, 88, 106, 124, 142, 160, 177, 194, 212, 230, 247, 264, 282, and 300 or a functional sequence variant thereof having at least 70%, at least

75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences (i) according to SEQ ID NOs: 64 - 66; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 82 - 84; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iii) according to SEQ ID NOs: 136 - 138; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) according to SEQ ID NOs: 154 - 156; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (v) according to SEQ ID NOs: 206 - 208; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) according to SEQ ID NOs: 224 - 226; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vii) according to SEQ ID NOs: 258 - 260; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (viii) according to SEQ ID NOs: 276 - 278; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ix) according to SEQ ID NOs: 294 - 296; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (x) according to SEQ ID NOs: 28 - 30;

or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (xi) according to SEQ ID NOs: 46 – 48; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (xii) according to SEQ ID NOs: 100 - 102; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (xiii) according to SEQ ID NOs: 118 - 120; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (xiv) according to SEQ ID NOs: 172 - 174; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (xv) according to SEQ ID NOs: 188 - 190; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xvi) according to SEQ ID NOs: 242 - 244; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 64 – 68 and 70; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 64 – 67 and 69 – 70; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iii) according to SEQ ID NOs: 82 – 86 and 88; or functional sequence variants thereof having at least 70%, at least 75%, at least

80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) according to SEQ ID NOs: 82 – 85 and 87 – 88; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (v) according to SEQ ID NOs: 136 – 140 and 142; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) according to SEQ ID NOs: 136 – 139 and 141 – 142; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vii) according to SEQ ID NOs: 154 – 158 and 160; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (viii) according to SEQ ID NOs: 154 – 157 and 159 – 160; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ix) according to SEQ ID NOs: 206 – 210 and 212; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (x) according to SEQ ID NOs: 206 – 209 and 211 – 212; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xi) according to SEQ ID NOs: 224 – 228 and 230; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xii) according to SEQ ID NOs: 224 – 227 and 229 – 230; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xiii) according to SEQ ID NOs: 258 – 262 and 264; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least

96%, at least 97%, at least 98% or at least 99% sequence identity; or (xiv) according to SEQ ID NOs: 258 – 261 and 263 – 264; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xv) according to SEQ ID NOs: 276 – 280 and 282; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xvi) according to SEQ ID NOs: 276 – 279 and 281 – 282; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xvii) according to SEQ ID NOs: 294 – 298 and 300; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xviii) according to SEQ ID NOs: 294 – 297 and 299 – 300; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xix) according to SEQ ID NOs: 28 – 32 and 34; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xx) according to SEQ ID NOs: 28 – 31 and 33 – 34; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxi) according to SEQ ID NOs: 46 – 50 and 52; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxii) according to SEQ ID NOs: 46 – 49 and 51 – 52; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxiii) according to SEQ ID NOs: 100 - 104 and 106; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;

or (xxiv) according to SEQ ID NOs: 100 – 103 and 105 – 106; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxv) according to SEQ ID NOs: 118 – 122 and 124; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxvi) according to SEQ ID NOs: 118 – 121 and 123 – 124; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxvii) according to SEQ ID NOs: 172 – 176 and 178; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxviii) according to SEQ ID NOs: 172 – 177; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxix) according to SEQ ID NOs: 188 – 192 and 194; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxx) according to SEQ ID NOs: 188 – 191 and 193 – 194; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xxxi) according to SEQ ID NOs: 242 – 247; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 64 – 68 and 70, respectively; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (ii) according to

SEQ ID NOs: 64 – 67 and 69 – 70; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

- 5 More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 224 – 228 and 230; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at
10 least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 224 – 227 and 229 – 230; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.
- 15 Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 276 – 280 and 282; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at
20 least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 276 – 279 and 281 – 282; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.
- 25 Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 206 – 210 and 212; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at
30 least 97%, at least 98% or at least 99% sequence identity; or (ii) according to SEQ ID NOs: 206 – 209 and 211 – 212; or functional sequence variants thereof having at least 70%, at

least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Particularly preferably, the antibody, or the antigen binding fragment thereof, according to
5 the present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 136 – 140 and 142; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 136
10 – 139 and 141 – 142; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Most preferably, the antibody, or the antigen binding fragment thereof, according to the
15 present invention comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 82 – 86 and 88; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) according to SEQ ID NOs: 82
20 – 85 and 87 – 88; or functional sequence variants thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

In addition, it is also preferred that the antibody, or the antigen binding fragment thereof,
25 according to the present invention comprises a heavy chain variable region (VH) and, optionally, a light chain variable region (VL), wherein the heavy chain variable region (VH) comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 35, 53, 71, 89, 107, 125, 143, 161, 178, 195, 213, 231, 248, 265, 283, and 301; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least
30 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises (i) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 71 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 72 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 89 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 90 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 143 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 144 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 161 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 162 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (v) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 213 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at

least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 214 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 231 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 232 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 265 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 266 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (viii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 283 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 284 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (ix) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 301 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 302 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at

least 99% sequence identity; or (x) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 35 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 36 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xi) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 53 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 54 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 107 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 108 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xiii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 125 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 126 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xiv) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 178 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light

- chain variable region (VL) amino acid sequence according to SEQ ID NO: 179 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xv) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 195 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 196 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (xvi) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 248 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 249 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.
- 20 More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 71 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 72 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.
- 30 More preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 231 or a functional sequence variant thereof having at least 70%,

at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 232 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Even more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 283 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 284 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Still more preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 213 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 214 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

Particularly preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 143 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light

chain variable region (VL) amino acid sequence according to SEQ ID NO: 144 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

5

Most preferably, the antibody, or the antigen binding fragment thereof, according to the present invention comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 89 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%,
10 at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 90 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

15

Preferably, the antibody, or the antigen binding fragment thereof, according to the present invention is gMGG1, gMGG2, gMGG3, gMGG4, gMGG8, gMGH1, gMGH2, gMGH3, gMGU1, gMGU3, gMGU5, gMGU8, gMGU10, gMGU11, gMGU12 or gMGV3, preferably the antibody, or the antigen binding fragment thereof, is gMGG3, gMGG4, gMGH2, gMGU5,
20 gMGU8 or gMGU12, more preferably the antibody, or the antigen binding fragment thereof, is gMGG4 or gMGH2.

The present inventors have isolated monoclonal antibody (mAb) according to the present invention, which are referred to herein as MGG1, MGG2, MGG3, MGG4, MGG8, MGH1, MGH2, MGH3, MGU1, MGU3, MGU5, MGU8, MGU10, MGU11, MGU12 and MGV3 (cf.
25 Tables 1 and 2, Example 1). Based on those antibodies, in particular on the VH and VL genes of those antibodies, the terms "gMGG1", "gMGG2", "gMGG3", "gMGG4", "gMGG8", "gMGH1", "gMGH2", "gMGH3", "gMGU1", "gMGU3", "gMGU5", "gMGU8", "gMGU10", "gMGU11", "gMGU12", and "gMGV3", as used herein, refer to the respective "generic"
30 antibodies, or antigen binding fragments thereof.

Namely, "gMGG1" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 28, a CDRH2 amino acid sequence according to SEQ ID NO: 29, a CDRH3 amino acid sequence according to SEQ ID NO: 30, a CDRL1 amino acid sequence according to SEQ ID NO: 31, a CDRL2 amino acid sequence according to SEQ ID NO: 32 or 33, and a CDRL3 amino acid sequence according to SEQ ID NO: 34. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 35 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 36.

- 10 "gMGG2" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 46, a CDRH2 amino acid sequence according to SEQ ID NO: 47, a CDRH3 amino acid sequence according to SEQ ID NO: 48, a CDRL1 amino acid sequence according to SEQ ID NO: 49, a CDRL2 amino acid sequence according to SEQ ID NO: 50 or 51, and a CDRL3 amino acid sequence according to SEQ ID NO: 52.
- 15 The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 53 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 54.

- "gMGG3" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 64, a CDRH2 amino acid sequence according to SEQ ID NO: 65, a CDRH3 amino acid sequence according to SEQ ID NO: 66, a CDRL1 amino acid sequence according to SEQ ID NO: 67, a CDRL2 amino acid sequence according to SEQ ID NO: 68 or 69, and a CDRL3 amino acid sequence according to SEQ ID NO: 70. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 71 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 72.
- 20
- 25

- "gMGG4" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 82, a CDRH2 amino acid sequence according to SEQ ID NO: 83, a CDRH3 amino acid sequence according to SEQ ID NO: 84, a CDRL1 amino acid sequence according to SEQ ID NO: 85, a CDRL2 amino acid sequence according to SEQ ID NO: 86 or 87, and a CDRL3 amino acid sequence according to SEQ ID NO: 88.
- 30

The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 89 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 90.

5 “gMGG8” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 100, a CDRH2 amino acid sequence according to SEQ ID NO: 101, a CDRH3 amino acid sequence according to SEQ ID NO: 102, a CDRL1 amino acid sequence according to SEQ ID NO: 103, a CDRL2 amino acid sequence according to SEQ ID NO: 104 or 105, and a CDRL3 amino acid sequence according to SEQ
10 ID NO: 106. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 107 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 108.

“gMGH1” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino
15 acid sequence according to SEQ ID NO: 118, a CDRH2 amino acid sequence according to SEQ ID NO: 119, a CDRH3 amino acid sequence according to SEQ ID NO: 120, a CDRL1 amino acid sequence according to SEQ ID NO: 121, a CDRL2 amino acid sequence according to SEQ ID NO: 122 or 123, and a CDRL3 amino acid sequence according to SEQ ID NO: 124. The heavy chain variable region (V_H) has preferably an amino acid sequence
20 according to SEQ ID NO: 125 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 126.

“gMGH2” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 136, a CDRH2 amino acid sequence according to
25 SEQ ID NO: 137, a CDRH3 amino acid sequence according to SEQ ID NO: 138, a CDRL1 amino acid sequence according to SEQ ID NO: 139, a CDRL2 amino acid sequence according to SEQ ID NO: 140 or 141, and a CDRL3 amino acid sequence according to SEQ ID NO: 142. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 143 and the light chain variable region (V_L) has preferably an amino
30 acid sequence according to SEQ ID NO: 144.

“gMGH3” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 154, a CDRH2 amino acid sequence according to SEQ ID NO: 155, a CDRH3 amino acid sequence according to SEQ ID NO: 156, a CDRL1 amino acid sequence according to SEQ ID NO: 157, a CDRL2 amino acid sequence according to SEQ ID NO: 158 or 159, and a CDRL3 amino acid sequence according to SEQ ID NO: 160. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 161 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 162.

“gMGU1” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 172, a CDRH2 amino acid sequence according to SEQ ID NO: 173, a CDRH3 amino acid sequence according to SEQ ID NO: 174, a CDRL1 amino acid sequence according to SEQ ID NO: 175, a CDRL2 amino acid sequence according to SEQ ID NO: 176, and a CDRL3 amino acid sequence according to SEQ ID NO: 177. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 178 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 179.

“gMGU3” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 188, a CDRH2 amino acid sequence according to SEQ ID NO: 189, a CDRH3 amino acid sequence according to SEQ ID NO: 190, a CDRL1 amino acid sequence according to SEQ ID NO: 191, a CDRL2 amino acid sequence according to SEQ ID NO: 192 or 193, and a CDRL3 amino acid sequence according to SEQ ID NO: 194. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 195 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 196.

“gMGU5” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 206, a CDRH2 amino acid sequence according to SEQ ID NO: 207, a CDRH3 amino acid sequence according to SEQ ID NO: 208, a CDRL1 amino acid sequence according to SEQ ID NO: 209, a CDRL2 amino acid sequence according to SEQ ID NO: 210 or 211, and a CDRL3 amino acid sequence according to SEQ

ID NO: 212. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 213 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 214.

5 "gMGU8" refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 224, a CDRH2 amino acid sequence according to SEQ ID NO: 225, a CDRH3 amino acid sequence according to SEQ ID NO: 226, a CDRL1 amino acid sequence according to SEQ ID NO: 227, a CDRL2 amino acid sequence according to SEQ ID NO: 228 or 229, and a CDRL3 amino acid sequence according to SEQ
10 ID NO: 230. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 231 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 232.

"gMGU10" refers to an antibody, or antigen binding fragment thereof, having a CDRH1
15 amino acid sequence according to SEQ ID NO: 242, a CDRH2 amino acid sequence according to SEQ ID NO: 243, a CDRH3 amino acid sequence according to SEQ ID NO: 244, a CDRL1 amino acid sequence according to SEQ ID NO: 245, a CDRL2 amino acid sequence according to SEQ ID NO: 246, and a CDRL3 amino acid sequence according to SEQ ID NO: 247. The heavy chain variable region (V_H) has preferably an amino acid
20 sequence according to SEQ ID NO: 248 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 249.

"gMGU11" refers to an antibody, or antigen binding fragment thereof, having a CDRH1
25 amino acid sequence according to SEQ ID NO: 258, a CDRH2 amino acid sequence according to SEQ ID NO: 259, a CDRH3 amino acid sequence according to SEQ ID NO: 260, a CDRL1 amino acid sequence according to SEQ ID NO: 261, a CDRL2 amino acid sequence according to SEQ ID NO: 262 or 263, and a CDRL3 amino acid sequence according to SEQ ID NO: 264. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 265 and the light chain variable region (V_L) has
30 preferably an amino acid sequence according to SEQ ID NO: 266.

“gMGU12” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 276, a CDRH2 amino acid sequence according to SEQ ID NO: 277, a CDRH3 amino acid sequence according to SEQ ID NO: 278, a CDRL1 amino acid sequence according to SEQ ID NO: 279, a CDRL2 amino acid sequence according to SEQ ID NO: 280 or 281, and a CDRL3 amino acid sequence according to SEQ ID NO: 282. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 283 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 284.

“gMGV3” refers to an antibody, or antigen binding fragment thereof, having a CDRH1 amino acid sequence according to SEQ ID NO: 294, a CDRH2 amino acid sequence according to SEQ ID NO: 295, a CDRH3 amino acid sequence according to SEQ ID NO: 296, a CDRL1 amino acid sequence according to SEQ ID NO: 297, a CDRL2 amino acid sequence according to SEQ ID NO: 298 or 299, and a CDRL3 amino acid sequence according to SEQ ID NO: 300. The heavy chain variable region (V_H) has preferably an amino acid sequence according to SEQ ID NO: 301 and the light chain variable region (V_L) has preferably an amino acid sequence according to SEQ ID NO: 302.

Optional additional features of the antibodies

Antibodies of the invention (i.e. antibodies binding to *P. falciparum* sporozoites and antibodies binding to the peptide of the invention), and antigen-binding fragments thereof, may be coupled, for example, to a drug for delivery to a treatment site or coupled to a detectable label to facilitate imaging of a site comprising cells of interest. Methods for coupling antibodies to drugs and detectable labels are well known in the art, as are methods for imaging using detectable labels. Labeled antibodies may be employed in a wide variety of assays, employing a wide variety of labels. Detection of the formation of an antibody-antigen complex, for example between an antibody of the invention and an epitope of interest or between the peptide or protein according to the invention and an antibody, can be facilitated by attaching a detectable substance to the antibody. Suitable detection means include the use of labels such as radionuclides, enzymes, coenzymes, fluorescers,

chemilumescers, chromogens, enzyme substrates or co-factors, enzyme inhibitors, prosthetic group complexes, free radicals, particles, dyes, and the like. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material is luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S , or ^3H . Such labeled reagents may be used in a variety of well-known assays, such as radioimmunoassays, enzyme immunoassays, e.g., ELISA, fluorescent immunoassays, and the like. Labeled antibodies according to the present invention may be thus be used in such assays for example as described in US 3,766,162; US 3,791,932; US 3,817,837; and US 4,233,402.

An antibody according to the invention may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent, or a radioactive metal ion or radioisotope. Examples of radioisotopes include, but are not limited to, I-^{131} , I-^{123} , I-^{125} , Y-^{90} , Re-^{188} , Re-^{186} , At-^{211} , Cu-^{67} , Bi-^{212} , Bi-^{213} , Pd-^{109} , Tc-^{99} , In-^{111} , and the like. Such antibody conjugates can be used for modifying a given biological response; the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin.

Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon et al. (1985) "Monoclonal Antibodies for Immunotargeting of Drugs in Cancer Therapy," in *Monoclonal Antibodies and Cancer Therapy*, ed. Reisfeld et al. (Alan R. Liss, Inc.), pp. 243-256; ed. Hellstrom et al. (1987) "Antibodies for Drug Delivery," in *Controlled Drug Delivery*, ed. Robinson et al. (2d ed; Marcel Dekker, Inc.), pp. 623-653; Thorpe (1985) "Antibody Carriers of Cytotoxic Agents in Cancer Therapy: A Review," in *Monoclonal Antibodies '84: Biological and Clinical Applications*, ed. Pinchera et al. pp. 475-506 (Editrice Kurtis, Milano, Italy, 1985); "Analysis, Results, and Future Prospective of the Therapeutic Use of Radiolabeled Antibody in Cancer Therapy," in *Monoclonal Antibodies*

for Cancer Detection and Therapy, ed. Baldwin et al. (Academic Press, New York, 1985), pp. 303-316; and Thorpe et al. (1982) Immunol. Rev. 62:119-158.

Alternatively, an antibody, or antibody fragment thereof, can be conjugated to a second
5 antibody, or antibody fragment thereof, to form an antibody heteroconjugate as described in
US 4,676,980. In addition, linkers may be used between the labels and the antibodies of the
invention, *e.g.*, as described in US 4,831,175. Antibodies or, antigen-binding fragments
thereof may be directly labeled with radioactive iodine, indium, yttrium, or other radioactive
particle known in the art, *e.g.*, as described in US 5,595,721. Treatment may consist of a
10 combination of treatment with conjugated and non-conjugated antibodies administered
simultaneously or subsequently *e.g.*, as described in WO00/52031; WO00/52473.

Antibodies of the invention may also be attached to a solid support. Additionally, antibodies
of the invention, or functional antibody fragments thereof, can be chemically modified by
15 covalent conjugation to a polymer to, for example, increase their circulating half-life.
Examples of polymers, and methods to attach them to peptides, are shown in US 4,766,106;
US 4,179,337; US 4,495,285 and US 4,609,546. In some embodiments the polymers may be
selected from polyoxyethylated polyols and polyethylene glycol (PEG). PEG is soluble in
water at room temperature and has the general formula: $R(O-CH_2-CH_2)_nO-R$, wherein R can
20 be hydrogen, or a protective group such as an alkyl or alkanol group. Preferably, the
protective group may have between 1 and 8 carbons. For example, the protective group is
methyl. The symbol n is a positive integer. In one embodiment n is between 1 and 1,000. In
another embodiment n is between 2 and 500. Preferably, the PEG has an average molecular
weight between 1,000 and 40,000, more preferably the PEG has a molecular weight between
25 2,000 and 20,000, even more preferably the PEG has a molecular weight between 3,000 and
12,000. Furthermore, PEG may have at least one hydroxy group, for example the PEG may
have a terminal hydroxy group. For example, it is the terminal hydroxy group which is
activated to react with a free amino group on the inhibitor. However, it will be understood
that the type and amount of the reactive groups may be varied to achieve a covalently
30 conjugated PEG/antibody of the present invention.

Water-soluble polyoxyethylated polyols are also useful in the present invention. They include polyoxyethylated sorbitol, polyoxyethylated glucose, polyoxyethylated glycerol (POG), and the like. In one embodiment, POG is used. Without being bound by any theory, because the glycerol backbone of polyoxyethylated glycerol is the same backbone occurring naturally in, for example, animals and humans in mono-, di-, triglycerides, this branching would not necessarily be seen as a foreign agent in the body. POG may have a molecular weight in the same range as PEG. Another drug delivery system that can be used for increasing circulatory half-life is the liposome. Methods of preparing liposome delivery systems are known to one of skill in the art. Other drug delivery systems are known in the art and are described in, for example, referenced in Poznansky MJ and Juliano RL, 1984, Pharmacol. Rev. 36(4): 277-336.

Antibodies of the invention may be provided in purified form. Typically, the antibody will be present in a composition that is substantially free of other polypeptides *e.g.*, where less than 90% (by weight), usually less than 60% and more usually less than 50% of the composition is made up of other polypeptides.

Antibodies of the invention may be immunogenic in non-human (or heterologous) hosts *e.g.*, in mice. In particular, the antibodies may have an idiotope that is immunogenic in non-human hosts, but not in a human host. In particular, antibodies of the invention for human use include those that cannot be easily isolated from hosts such as mice, goats, rabbits, rats, non-primate mammals, etc. and cannot generally be obtained by humanization or from xeno-mice.

Production of Antibodies

Antibodies according to the invention can be made by any method known in the art. For example, the general methodology for making monoclonal antibodies using hybridoma technology is well known (Kohler, G. and Milstein, C., 1975; Kozbar et al. 1983).

Preferably, the EBV immortalization method described in WO2004/076677 is used. In this method B cells producing the antibody of the invention are transformed with EBV and a

polyclonal B cell activator. Additional stimulants of cellular growth and differentiation may optionally be added during the transformation step to further enhance the efficiency. These stimulants may be cytokines such as IL-2 and IL-15. In one aspect, IL-2 is added during the immortalization step to further improve the efficiency of immortalization, but its use is not essential. The immortalized B cells produced using these methods can then be cultured using methods known in the art and antibodies isolated therefrom.

Another preferred method is described in WO 2010/046775. In this method plasma cells are cultured in limited numbers, or as single plasma cells in microwell culture plates. Antibodies can be isolated from the plasma cell cultures. Further, from the plasma cell cultures, RNA can be extracted and PCR can be performed using methods known in the art. The VH and VL regions of the antibodies can be amplified by RT-PCR (reverse transcriptase PCR), sequenced and cloned into an expression vector that is then transfected into HEK293T cells or other host cells. The cloning of nucleic acid in expression vectors, the transfection of host cells, the culture of the transfected host cells and the isolation of the produced antibody can be done using any methods known to one of skill in the art.

The antibodies may be further purified, if desired, using filtration, centrifugation and various chromatographic methods such as HPLC or affinity chromatography. Techniques for purification of antibodies, *e.g.*, monoclonal antibodies, including techniques for producing pharmaceutical-grade antibodies, are well known in the art.

Fragments of the antibodies of the invention can be obtained from the antibodies by methods that include digestion with enzymes, such as pepsin or papain, and/or by cleavage of disulfide bonds by chemical reduction. Alternatively, fragments of the antibodies can be obtained by cloning and expression of part of the sequences of the heavy or light chains. Antibody "fragments" include Fab, Fab', F(ab')₂ and Fv fragments. The invention also encompasses single-chain Fv fragments (scFv) derived from the heavy and light chains of an antibody of the invention. For example, the invention includes a scFv comprising the CDRs from an antibody of the invention. Also included are heavy or light chain monomers and dimers, single domain heavy chain antibodies, single domain light chain antibodies, as well as single chain

antibodies, e.g., single chain Fv in which the heavy and light chain variable domains are joined by a peptide linker.

Antibody fragments of the invention may impart monovalent or multivalent interactions and
5 be contained in a variety of structures as described above. For instance, scFv molecules may
be synthesized to create a trivalent "triabody" or a tetravalent "tetrabody." The scFv molecules
may include a domain of the Fc region resulting in bivalent minibodies. In addition, the
sequences of the invention may be a component of multispecific molecules in which the
sequences of the invention target the epitopes of the invention and other regions of the
10 molecule bind to other targets. Exemplary molecules include, but are not limited to,
bispecific Fab2, trispecific Fab3, bispecific scFv, and diabodies (Holliger and Hudson, 2005,
Nature Biotechnology 9: 1126-1136).

Standard techniques of molecular biology may be used to prepare DNA sequences encoding
15 the antibodies or antibody fragments of the present invention. Desired DNA sequences may
be synthesized completely or in part using oligonucleotide synthesis techniques. Site-directed
mutagenesis and polymerase chain reaction (PCR) techniques may be used as appropriate.

Any suitable host cell/vector system may be used for expression of the DNA sequences
20 encoding the antibody molecules of the present invention or fragments thereof. Bacterial, for
example *E. coli*, and other microbial systems may be used, in part, for expression of antibody
fragments such as Fab and F(ab')₂ fragments, and especially Fv fragments and single chain
antibody fragments, for example, single chain Fvs. Eukaryotic, e.g., mammalian, host cell
expression systems may be used for production of larger antibody molecules, including
25 complete antibody molecules. Suitable mammalian host cells include, but are not limited to,
CHO, HEK293T, PER.C6, NS0, myeloma or hybridoma cells.

The present invention also provides a process for the production of an antibody molecule
according to the present invention comprising culturing a host cell comprising a vector
30 encoding a nucleic acid of the present invention under conditions suitable for expression of
protein from DNA encoding the antibody molecule of the present invention, and isolating the
antibody molecule.

- The antibody molecule may comprise only a heavy or light chain polypeptide, in which case only a heavy chain or light chain polypeptide coding sequence needs to be used to transfect the host cells. For production of products comprising both heavy and light chains, the cell
- 5 line may be transfected with two vectors, a first vector encoding a light chain polypeptide and a second vector encoding a heavy chain polypeptide. Alternatively, a single vector may be used, the vector including sequences encoding light chain and heavy chain polypeptides. Alternatively, antibodies according to the invention may be produced by (i) expressing a nucleic acid sequence according to the invention in a host cell, e.g. by use of a vector
- 10 according to the present invention, and (ii) isolating the expressed antibody product. Additionally, the method may include (iii) purifying the isolated antibody. Transformed B cells and cultured plasma cells may be screened for those producing antibodies of the desired specificity or function.
- 15 The screening step may be carried out by any immunoassay, e.g., ELISA, by staining of tissues or cells (including transfected cells), by neutralization assay or by one of a number of other methods known in the art for identifying desired specificity or function. The assay may select on the basis of simple recognition of one or more antigens, or may select on the additional basis of a desired function e.g., to select neutralizing antibodies rather than just antigen-
- 20 binding antibodies, to select antibodies that can change characteristics of targeted cells, such as their signaling cascades, their shape, their growth rate, their capability of influencing other cells, their response to the influence by other cells or by other reagents or by a change in conditions, their differentiation status, etc.
- 25 Individual transformed B cell clones may then be produced from the positive transformed B cell culture. The cloning step for separating individual clones from the mixture of positive cells may be carried out using limiting dilution, micromanipulation, single cell deposition by cell sorting or another method known in the art.
- 30 Nucleic acid from the cultured plasma cells can be isolated, cloned and expressed in HEK293T cells or other known host cells using methods known in the art.

The immortalized B cell clones or the transfected host-cells of the invention can be used in various ways e.g., as a source of monoclonal antibodies, as a source of nucleic acid (DNA or mRNA) encoding a monoclonal antibody of interest, for research, etc.

- 5 The invention also provides a composition comprising immortalized B memory cells or transfected host cells that produce antibodies according to the present invention.

The immortalized B cell clone or the cultured plasma cells of the invention may also be used as a source of nucleic acid for the cloning of antibody genes for subsequent recombinant
10 expression. Expression from recombinant sources is more common for pharmaceutical purposes than expression from B cells or hybridomas e.g., for reasons of stability, reproducibility, culture ease, etc.

Thus the invention also provides a method for preparing a recombinant cell, comprising the
15 steps of: (i) obtaining one or more nucleic acids (e.g., heavy and/or light chain mRNAs) from the B cell clone or the cultured plasma cells that encodes the antibody of interest; (ii) inserting the nucleic acid into an expression vector and (iii) transfecting the vector into a host cell in order to permit expression of the antibody of interest in that host cell.

20 Similarly, the invention provides a method for preparing a recombinant cell, comprising the steps of: (i) sequencing nucleic acid(s) from the B cell clone or the cultured plasma cells that encodes the antibody of interest; and (ii) using the sequence information from step (i) to prepare nucleic acid(s) for insertion into a host cell in order to permit expression of the antibody of interest in that host cell. The nucleic acid may, but need not, be manipulated
25 between steps (i) and (ii) to introduce restriction sites, to change codon usage, and/or to optimize transcription and/or translation regulatory sequences.

Furthermore, the invention also provides a method of preparing a transfected host cell, comprising the step of transfecting a host cell with one or more nucleic acids that encode an
30 antibody of interest, wherein the nucleic acids are nucleic acids that were derived from an immortalized B cell clone or a cultured plasma cell of the invention. Thus the procedures for

first preparing the nucleic acid(s) and then using it to transfect a host cell can be performed at different times by different people in different places (e.g., in different countries).

5 These recombinant cells of the invention can then be used for expression and culture purposes. They are particularly useful for expression of antibodies for large-scale pharmaceutical production. They can also be used as the active ingredient of a pharmaceutical composition. Any suitable culture technique can be used, including but not limited to static culture, roller bottle culture, ascites fluid, hollow-fiber type bioreactor cartridge, modular minifermenter, stirred tank, microcarrier culture, ceramic core perfusion,
10 etc.

Methods for obtaining and sequencing immunoglobulin genes from B cells or plasma cells are well known in the art (e.g., see Chapter 4 of Kuby Immunology, 4th edition, 2000).

15 The transfected host cell may be a eukaryotic cell, including yeast and animal cells, particularly mammalian cells (e.g., CHO cells, NS0 cells, human cells such as PER.C6 or HKB-11 cells, myeloma cells, or a human liver cell), as well as plant cells, whereby mammalian cells are preferred. Preferred expression hosts can glycosylate the antibody of the invention, particularly with carbohydrate structures that are not themselves immunogenic in
20 humans. In one embodiment the transfected host cell may be able to grow in serum-free media. In a further embodiment the transfected host cell may be able to grow in culture without the presence of animal-derived products. The transfected host cell may also be cultured to give a cell line.

25 The invention also provides a method for preparing one or more nucleic acid molecules (*e.g.*, heavy and light chain genes) that encode an antibody of interest, comprising the steps of: (i) preparing an immortalized B cell clone or culturing plasma cells according to the invention; (ii) obtaining from the B cell clone or the cultured plasma cells nucleic acid that encodes the antibody of interest. Further, the invention provides a method for obtaining a
30 nucleic acid sequence that encodes an antibody of interest, comprising the steps of: (i) preparing an immortalized B cell clone or culturing plasma cells according to the invention;

(ii) sequencing nucleic acid from the B cell clone or the cultured plasma cells that encodes the antibody of interest.

The invention further provides a method of preparing nucleic acid molecule(s) that encode an antibody of interest, comprising the step of obtaining the nucleic acid that was obtained from a transformed B cell clone or cultured plasma cells of the invention. Thus the procedures for first obtaining the B cell clone or the cultured plasma cell, and then obtaining nucleic acid(s) from the B cell clone or the cultured plasma cells can be performed at different times by different people in different places (e.g., in different countries).

The invention also comprises a method for preparing an antibody (e.g., for pharmaceutical use) according to the present invention, comprising the steps of: (i) obtaining and/or sequencing one or more nucleic acids (e.g., heavy and light chain genes) from the selected B cell clone or the cultured plasma cells expressing the antibody of interest; (ii) inserting the nucleic acid(s) into or using the nucleic acid(s) sequence(s) to prepare an expression vector; (iii) transfecting a host cell that can express the antibody of interest; (iv) culturing or sub-culturing the transfected host cells under conditions where the antibody of interest is expressed; and, optionally, (v) purifying the antibody of interest.

The invention also provides a method of preparing an antibody comprising the steps of: culturing or sub-culturing a transfected host cell population, e.g. a stably transfected host cell population, under conditions where the antibody of interest is expressed and, optionally, purifying the antibody of interest, wherein said transfected host cell population has been prepared by (i) providing nucleic acid(s) encoding a selected antibody of interest that is produced by a B cell clone or cultured plasma cells prepared as described above, (ii) inserting the nucleic acid(s) into an expression vector, (iii) transfecting the vector in a host cell that can express the antibody of interest, and (iv) culturing or sub-culturing the transfected host cell comprising the inserted nucleic acids to produce the antibody of interest. Thus the procedures for first preparing the recombinant host cell and then culturing it to express antibody can be performed at very different times by different people in different places (e.g., in different countries).

Nucleic acid molecules, vectors and cells

In another aspect, the invention also provides a nucleic acid molecule comprising a polynucleotide encoding the antibody, or the antigen binding fragment thereof, according to the present invention as described above. In another aspect, the present invention also provides a nucleic acid molecule comprising a polynucleotide encoding the peptide according to the present invention as described above or the protein according to the present invention as described above.

Examples of nucleic acid molecules and/or polynucleotides include, e.g., a recombinant polynucleotide, a vector, an oligonucleotide, an RNA molecule such as an rRNA, an mRNA, an miRNA, an siRNA, or a tRNA, or a DNA molecule such as a cDNA. The nucleic acid molecule may also be a vector as described below.

A nucleic acid molecule is a molecule comprising, preferably consisting of nucleic acid components. The term nucleic acid molecule preferably refers to DNA or RNA molecules. In particular, it is used synonymous with the term "polynucleotide". Preferably, a nucleic acid molecule is a polymer comprising or consisting of nucleotide monomers which are covalently linked to each other by phosphodiester-bonds of a sugar/phosphate-backbone. The term "nucleic acid molecule" also encompasses modified nucleic acid molecules, such as base-modified, sugar-modified or backbone-modified etc. DNA or RNA molecules.

Regarding nucleic acid molecules comprising a polynucleotide encoding the antibody according to the present invention, such nucleic acid sequences, which encode part or all of the light and heavy chains and CDRs of the antibodies of the present invention are preferred. Preferably provided herein are thus nucleic acid sequences encoding part or all of the light and heavy chains, in particular VH and VL sequences and CDRs of the exemplary antibodies of the invention. Tables 1 and 2 provide the SEQ ID numbers for the amino acid sequences of the CDRs and VH and VL of exemplary antibodies according to the present invention.

Tables 3 and 4 below provides the SEQ ID numbers for exemplary nucleic acid sequences encoding the CDRs and VH and VL of exemplary antibodies according to the present invention. Due to the redundancy of the genetic code, the present invention also comprises sequence variants of these nucleic acid sequences and in particular such sequence variants, which encode the same amino acid sequences.

Table 3 below shows the SEQ ID NOs of the nucleic acid sequences of the heavy chain CDR's (CDRH1, CDRH2, and CDRH3) and of the heavy chain variable region (referred to as "VH") of exemplary antibodies according to the present invention:

Antibody name	CDRH1	CDRH2	CDRH3	VH
MGG1	37	38	39	44
MGG2	55	56	57	62
MGG3	73	74	75	80
MGG4	91	92	93	98
MGG8	109	110	111	116
MGH1	127	128	129	134
MGH2	145	146	147	152
MGH3	163	164	165	170
MGU1	180	181	182	186
MGU3	197	198	199	204
MGU5	215	216	217	222
MGU8	233	234	235	240
MGU10	250	251	252	256
MGU11	267	268	269	274
MGU12	285	286	287	292
MGV3	303	304	305	310

Table 3.

Table 4 below shows the SEQ ID NOs of the nucleic acid sequences of the light chain CDR's (CDRL1, CDRL2, and CDRL3) and of the light chain variable region (referred to as "VL") of exemplary antibodies according to the present invention:

Antibody name	CDRL1	CDRL2	CDRL2 long	CDRL3	VL
MGG1	40	41	42	43	45
MGG2	58	59	60	61	63
MGG3	76	77	78	79	81
MGG4	94	95	96	97	99
MGG8	112	113	114	115	117
MGH1	130	131	132	133	135
MGH2	148	149	150	151	153
MGH3	166	167	168	169	171
MGU1	183	184	—	185	187
MGU3	200	201	202	203	205
MGU5	218	219	220	221	223
MGU8	236	237	238	239	241
MGU10	253	254	—	255	257
MGU11	270	271	272	273	275
MGU12	288	289	290	291	293
MGV3	306	307	308	309	311

5 Table 4.

Preferably, the sequence of the nucleic acid molecule according to the present invention comprises or consists of a polynucleotide sequence according to any one of SEQ ID NOs: 37 – 45, 55 – 63, 73 – 81, 91 – 99, 109 – 117, 127 – 135, 145 – 153, 163 – 171, 180 – 187, 197 – 205, 215 – 223, 233 – 241, 250 – 257, 267 – 275, 285 – 293, 303 – 311; or a functional sequence variant thereof. In other words, it is preferred that the nucleic acid molecule according to the present invention comprises a the polynucleotide sequence, which comprises or consists of a nucleic acid sequence according to any one of SEQ ID NOs: 37 – 45, 55 – 63, 73 – 81, 91 – 99, 109 – 117, 127 – 135, 145 – 153, 163 – 171, 180 – 187, 197 –

205, 215 – 223, 233 – 241, 250 – 257, 267 – 275, 285 – 293, 303 – 311; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

5

It is also preferred that nucleic acid sequences according to the invention include nucleic acid sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity to the nucleic acid encoding a CDR, a VH sequence and/or a VL sequence used in an (exemplary) antibody according to the present invention, for example to the sequences shown in Tables 3 and 4.

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It is also preferred that nucleic acid sequences according to the invention include nucleic acid sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity to the nucleic acid encoding a peptide according to the present invention, for example to the sequences according to any of SEQ ID NOs: 1 - 24. More preferably, the nucleic acid molecule according to the present invention comprises a the polynucleotide encoding any of the amino acid sequences according to any of SEQ ID NOs: 1 – 24.

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In general, the nucleic acid molecule may be manipulated to insert, delete or alter certain nucleic acid sequences. Changes from such manipulation include, but are not limited to, changes to introduce restriction sites, to amend codon usage, to add or optimize transcription and/or translation regulatory sequences, etc. It is also possible to change the nucleic acid to alter the encoded amino acids. For example, it may be useful to introduce one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) amino acid substitutions, deletions and/or insertions into the antibody's amino acid sequence. Such point mutations can modify effector functions, antigen-binding affinity, post-translational modifications, immunogenicity, etc., can introduce amino acids for the attachment of covalent groups (*e.g.*, labels) or can introduce tags (*e.g.*, for purification purposes). Mutations can be introduced in specific sites or can be introduced at random, followed by selection (*e.g.*, molecular evolution). For instance, one or more nucleic acids encoding any of the CDR regions, a VH sequence and/or a VL sequence

of an (exemplary) antibody of the invention can be randomly or directionally mutated to introduce different properties in the encoded amino acids. Such changes can be the result of an iterative process wherein initial changes are retained and new changes at other nucleotide positions are introduced. Further, changes achieved in independent steps may be combined.

5 Different properties introduced into the encoded amino acids may include, but are not limited to, enhanced affinity.

10 In another aspect the present invention also provides a vector, for example an expression vector, comprising a nucleic acid molecule according to the present invention. Preferably, a vector comprises a nucleic acid molecule as described above.

The term "vector" refers to a nucleic acid molecule, preferably to a recombinant nucleic acid molecule, i.e. a nucleic acid molecule which does not occur in nature. A vector in the context
15 of the present invention is suitable for incorporating or harboring a desired nucleic acid sequence. Such vectors may be storage vectors, expression vectors, cloning vectors, transfer vectors etc. A storage vector is a vector which allows the convenient storage of a nucleic acid molecule. Thus, the vector may comprise a sequence corresponding, e.g., to a desired antibody or antibody fragment thereof according to the present invention or to a desired
20 peptide or protein according to the present invention. An expression vector may be used for production of expression products such as RNA, e.g. mRNA, or peptides, polypeptides or proteins. For example, an expression vector may comprise sequences needed for transcription of a sequence stretch of the vector, such as a promoter sequence. A cloning vector is typically a vector that contains a cloning site, which may be used to incorporate nucleic acid
25 sequences into the vector. A cloning vector may be, e.g., a plasmid vector or a bacteriophage vector. A transfer vector may be a vector which is suitable for transferring nucleic acid molecules into cells or organisms, for example, viral vectors. A vector in the context of the present invention may be, e.g., an RNA vector or a DNA vector. Preferably, a vector is a DNA molecule. For example, a vector in the sense of the present application comprises a cloning
30 site, a selection marker, such as an antibiotic resistance factor, and a sequence suitable for multiplication of the vector, such as an origin of replication. Preferably, a vector in the context of the present application is a plasmid vector.

In a further aspect, the present invention also provides cell (a) expressing (i) the antibody, or the antigen binding fragment thereof, according to the present invention or (ii) the peptide or protein according to the present invention; and/or (b) comprising the vector according to the present invention.

Examples of such cells include but are not limited to, eukaryotic cells, e.g., yeast cells, animal cells or plant cells. Preferably, the cells are mammalian cells, more preferably a mammalian cell line. Preferred examples include human cells, CHO cells, HEK293T cells, PER.C6 cells, NS0 cells, human liver cells, myeloma cells or hybridoma cells.

In particular, the cell may be transfected with a vector according to the present invention, preferably with an expression vector. The term "transfection" refers to the introduction of nucleic acid molecules, such as DNA or RNA (e.g. mRNA) molecules, into cells, preferably into eukaryotic cells. In the context of the present invention, the term "transfection" encompasses any method known to the skilled person for introducing nucleic acid molecules into cells, preferably into eukaryotic cells, such as into mammalian cells. Such methods encompass, for example, electroporation, lipofection, e.g. based on cationic lipids and/or liposomes, calcium phosphate precipitation, nanoparticle based transfection, virus based transfection, or transfection based on cationic polymers, such as DEAE-dextran or polyethylenimine etc. Preferably, the introduction is non-viral.

Moreover, the cells of the present invention may be transfected stably or transiently with the vector according to the present invention, e.g. for expressing the antibody, or the antigen binding fragment thereof, according to the present invention or for expressing the peptide or protein according to the present invention. Preferably, the cells are stably transfected with the vector according to the present invention, for example encoding the antibody, or the antigen binding fragment thereof, according to the present invention or encoding the peptide or protein according to the present invention. Alternatively, it is also preferred that the cells are transiently transfected with the vector according to the present invention, for example

encoding the antibody, or the antigen binding fragment thereof, according to the present invention or encoding the peptide or protein according to the present invention.

5 Pharmaceutical composition

In a further aspect the present invention provides a pharmaceutical composition comprising one or more of:

- (i) the peptide according to the present invention;
- 10 (ii) the protein according to the present invention;
- (iii) the nucleic acid encoding the protein or the peptide according to the present invention;
- (iv) the virus-like particle according to the present invention;
- (v) the protein nanoparticle according to the present invention;
- 15 (vi) the antibody, or the antibody fragment thereof, according to the present invention;
- (vii) the nucleic acid encoding the antibody, or antibody fragments according to the present invention;
- (viii) the vector comprising the nucleic acid according to the present invention; and/or
- (ix) the cell expressing the antibody or the peptide according to the present invention, or
- 20 comprising the vector according to the present invention.

In other words, the present invention also provides a pharmaceutical composition comprising the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or the antigen binding fragment thereof, according to

25 the present invention, the nucleic acid according to the present invention, the vector according to the present invention and/or the cell according to the present invention.

Preferably, the pharmaceutical composition comprises the peptide according to the present invention and/or the protein according to the present invention.

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It is also preferred that the pharmaceutical composition comprises the virus-like particle according to the present invention and/or the protein nanoparticle according to the present invention.

5 In this context, i.e. if the pharmaceutical composition comprises the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention and/or the protein nanoparticle according to the present invention, the pharmaceutical composition is preferably a vaccine. A "vaccine" is typically understood to be a prophylactic or therapeutic material providing at least one antigen,
10 preferably an immunogen, such as the peptide according to the present invention. An "immunogen" is typically able to elicit an immune response. As used herein an "immunogen" is in particular a protein or a portion thereof that is capable of inducing an immune response in a mammal (such as humans and cattle, preferably cattle), such as a mammal infected or at risk of infection with a pathogen (such as *Plasmodium*). Administration of an immunogen can
15 for example lead to protective immunity and/or proactive immunity against a pathogen of interest. Accordingly, the antigen or immunogen can typically stimulate the body's adaptive immune system to provide an adaptive immune response. In particular, an "antigen" or an "immunogen" refers typically to a substance which may be recognized by the immune system, preferably by the adaptive immune system, and which is capable of triggering an
20 antigen-specific immune response, e.g. by formation of antibodies and/or antigen-specific T cells as part of an adaptive immune response. Typically, an antigen may be or may comprise a peptide or protein which may be presented by the MHC to T-cells.

Preferably, the pharmaceutical composition comprises the antibody, or the antibody fragment
25 thereof, according to the present invention.

It is also preferred that the composition comprises the nucleic acid according to the invention.

Preferably, the pharmaceutical composition comprises the vector according to the present
30 invention and/or the cell according to the present invention.

The pharmaceutical composition may preferably also contain a pharmaceutically acceptable carrier, diluent and/or excipient. Although the carrier or excipient may facilitate administration, it should preferably not itself induce the production of antibodies harmful to the individual receiving the composition. Nor should it be toxic. Suitable carriers may be

5 large, slowly metabolized macromolecules such as proteins, polypeptides, liposomes, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers and inactive virus particles. In general, pharmaceutically acceptable carriers in a pharmaceutical composition according to the present invention may be active components or inactive components. Preferably, the pharmaceutically acceptable carrier in a

10 pharmaceutical composition according to the present invention is not an active component in respect to malaria.

Pharmaceutically acceptable salts can be used, for example mineral acid salts, such as hydrochlorides, hydrobromides, phosphates and sulphates, or salts of organic acids, such as

15 acetates, propionates, malonates and benzoates.

Pharmaceutically acceptable carriers in a pharmaceutical composition may additionally contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents or pH buffering substances, may be present in such

20 compositions. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries and suspensions, for ingestion by the subject.

Pharmaceutical compositions of the invention may be prepared in various forms. For

25 example, the compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared (e.g., a lyophilized composition, similar to Synagis™ and Herceptin™, for reconstitution with sterile water containing a preservative). The composition may be prepared for topical administration e.g., as an ointment, cream or powder. The

30 composition may be prepared for oral administration e.g., as a tablet or capsule, as a spray, or as a syrup (optionally flavored). The composition may be prepared for pulmonary administration e.g., as an inhaler, using a fine powder or a spray. The composition may be

prepared as a suppository or pessary. The composition may be prepared for nasal, aural or ocular administration e.g., as drops. The composition may be in kit form, designed such that a combined composition is reconstituted just prior to administration to a subject. For example, a lyophilized antibody may be provided in kit form with sterile water or a sterile buffer.

5

It is preferred that the active ingredient in the composition is the antibody, or an antibody fragment thereof, according to the present invention. It is also preferred that the active ingredient in the composition is the peptide according to the present invention, the protein according to the present invention, the protein nanoparticle according to the present invention and/or the virus-like particle according to the present invention. As such, it (the antibody, the peptide, the protein, etc.) may be susceptible to degradation in the gastrointestinal tract. Thus, if the composition is to be administered by a route using the gastrointestinal tract, the composition may contain agents which protect the antibody, the peptide, the protein, the protein nanoparticle or the virus-like particle from degradation but which release it once it has been absorbed from the gastrointestinal tract.

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A thorough discussion of pharmaceutically acceptable carriers is available in Gennaro (2000) Remington: The Science and Practice of Pharmacy, 20th edition, ISBN: 0683306472.

Pharmaceutical compositions of the invention generally have a pH between 5.5 and 8.5, in some embodiments this may be between 6 and 8, and in other embodiments about 7. The pH may be maintained by the use of a buffer. The composition may be sterile and/or pyrogen free. The composition may be isotonic with respect to humans. In one embodiment pharmaceutical compositions of the invention are supplied in hermetically-sealed containers.

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Within the scope of the invention are compositions present in several forms of administration; the forms include, but are not limited to, those forms suitable for parenteral administration, e.g., by injection or infusion, for example by bolus injection or continuous infusion. Where the product is for injection or infusion, it may take the form of a suspension, solution or emulsion in an oily or aqueous vehicle and it may contain formulatory agents, such as suspending, preservative, stabilizing and/or dispersing agents. Alternatively, the antibody or the peptide/protein may be in dry form, for reconstitution before use with an appropriate

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sterile liquid. A vehicle is typically understood to be a material that is suitable for storing, transporting, and/or administering a compound, such as a pharmaceutically active compound, in particular the antibody or the peptide/protein according to the present invention. For example, the vehicle may be a physiologically acceptable liquid, which is
5 suitable for storing, transporting, and/or administering a pharmaceutically active compound, in particular the antibody or the peptide/protein according to the present invention. Once formulated, the compositions of the invention can be administered directly to the subject. In one embodiment the compositions are adapted for administration to mammalian, e.g., human subjects.

10

The pharmaceutical compositions of this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intraperitoneal, intrathecal, intraventricular, transdermal, transcutaneous, topical, subcutaneous, intranasal, enteral, sublingual, intravaginal or rectal routes.
15 Hyposprays may also be used to administer the pharmaceutical compositions of the invention. Preferably, the pharmaceutical composition may be prepared for oral administration, e.g. as tablets, capsules and the like, for topical administration, or as injectable, e.g. as liquid solutions or suspensions, whereby it is particularly preferred that the pharmaceutical composition is an injectable. Solid forms suitable for solution in, or
20 suspension in, liquid vehicles prior to injection are also preferred, e.g. that the pharmaceutical composition is in lyophilized form.

For injection, e.g. intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will preferably be in the form of a parenterally acceptable
25 aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilizers, buffers, antioxidants and/or other additives may be included, as required. Whether it is a polypeptide, peptide, or nucleic acid molecule, other
30 pharmaceutically useful compound according to the present invention that is to be given to an individual, administration is preferably in a "prophylactically effective amount" or a "therapeutically effective amount" (as the case may be), this being sufficient to show benefit

to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. For injection, the pharmaceutical composition according to the present invention may be provided for example in a pre-filled syringe.

5

The inventive pharmaceutical composition as defined above may also be administered orally in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient, i.e. the inventive transporter cargo conjugate molecule as defined above, is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

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The inventive pharmaceutical composition may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, e.g. including diseases of the skin or of any other accessible epithelial tissue. Suitable topical formulations are readily prepared for each of these areas or organs. For topical applications, the inventive pharmaceutical composition may be formulated in a suitable ointment, containing the inventive pharmaceutical composition, particularly its components as defined above, suspended or dissolved in one or more carriers. Carriers for topical administration include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the inventive pharmaceutical composition can be formulated in a suitable lotion or cream. In the context of the present invention, suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

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30 Dosage treatment may be a single dose schedule or a multiple dose schedule. In particular, the pharmaceutical composition may be provided as single-dose product. Preferably, the amount of the antibody or of the peptide/protein in the pharmaceutical composition – in

particular if provided as single-dose product – does not exceed 200 mg, more preferably does not exceed 100 mg, and even more preferably does not exceed 50 mg.

The pharmaceutical composition according to the present invention may be administered
5 once or repeatedly. For example, the pharmaceutical composition according to the present invention may be administered daily, e.g. once or several times per day, e.g. once, twice, three times or four times per day, preferably once or twice per day, more preferable once per day, for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 or more days, e.g. daily for 1, 2, 3, 4, 5, 6 months. Preferably, the pharmaceutical composition according
10 to the present invention may be administered weekly, e.g. once or twice per week, for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 or more weeks, e.g. weekly for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or weekly for 2, 3, 4, or 5 years. Moreover, the pharmaceutical composition according to the present invention may be preferably administered monthly, e.g. once per month or, more preferably, every second month for 1,
15 2, 3, 4, or 5 or more years. It is also preferred that the administration continues for the lifetime. In addition, one single administration only is also envisaged, in particular in respect to certain indications, e.g. for prevention of malaria in case of accidental exposure, e.g. in non-immunized subjects.

20 In particular, it is preferred that for a single dose, e.g. a daily, weekly or monthly dose, preferably for a weekly dose, the amount of the antibody or of the peptide/protein in the pharmaceutical composition according to the present invention, does not exceed 1 g, preferably does not exceed 500 mg, more preferably does not exceed 200 mg, even more preferably does not exceed 100 mg, and particularly preferably does not exceed 50 mg.

25

Pharmaceutical compositions typically include an “effective” amount of the antibody of the invention, or of the peptide/protein of the invention, i.e. an amount that is sufficient to treat, ameliorate, attenuate or prevent a desired disease or condition, or to exhibit a detectable therapeutic effect. Therapeutic effects also include reduction or attenuation in pathogenic
30 potency or physical symptoms. The precise effective amount for any particular subject will depend upon their size, weight, and health, the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. The effective amount

for a given situation is determined by routine experimentation and is within the judgment of a clinician. For purposes of the present invention, an effective dose will generally be from about 0.005 to about 100 mg/kg, preferably from about 0.0075 to about 50 mg/kg, more preferably from about 0.01 to about 10 mg/kg, and even more preferably from about 0.02 to about 5 mg/kg, of the antibody of the present invention (e.g. amount of the antibody in the pharmaceutical composition) in relation to the bodyweight (e.g., in kg) of the individual to which it is administered.

Moreover, the pharmaceutical composition according to the present invention may also comprise an additional active component, which may be a further antibody or a component, which is not an antibody. The additional active component is preferably a checkpoint inhibitor.

The antibody, or the antigen binding fragment, according to the present invention and/or the peptide/protein according to the present invention can be present either in the same pharmaceutical composition as the additional active component or, preferably, it can be comprised by a first pharmaceutical composition and the additional active component is comprised by a second pharmaceutical composition different from the first pharmaceutical composition. Accordingly, if more than one additional active component is envisaged, each additional active component and the antibody, or the antigen binding fragment, according to the present invention or the peptide/protein according to the present invention is preferably comprised by a different pharmaceutical composition. Such different pharmaceutical compositions may be administered either combined/simultaneously or at separate times or at separate locations (e.g. separate parts of the body).

Preferably, the antibody (or the peptide/protein) according to the present invention and the additional active component provide an additive therapeutic effect or, preferably, a synergistic therapeutic effect. The term "synergy" is used to describe a combined effect of two or more active agents that is greater than the sum of the individual effects of each respective active agent. Thus, where the combined effect of two or more agents results in "synergistic inhibition" of an activity or process, it is intended that the inhibition of the activity or process is greater than the sum of the inhibitory effects of each respective active agent. The term

“synergistic therapeutic effect” refers to a therapeutic effect observed with a combination of two or more therapies wherein the therapeutic effect (as measured by any of a number of parameters) is greater than the sum of the individual therapeutic effects observed with the respective individual therapies.

5

In one embodiment, a composition of the invention may include an antibody of the invention, wherein the antibodies may make up at least 50% by weight (*e.g.*, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more) of the total protein in the composition. In such a composition, the antibodies are preferably in purified form.

10

In another embodiment, a composition of the invention may include a peptide/protein of the invention, wherein the peptide/protein may make up at least 50% by weight (*e.g.*, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more) of the total protein in the composition. In such a composition, the peptides/proteins are preferably in purified form.

15

The present invention also provides a method of preparing a pharmaceutical composition comprising the steps of: (i) preparing an antibody or a peptide/protein of the invention; and (ii) admixing the purified antibody or the purified peptide/protein with one or more pharmaceutically-acceptable carriers.

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In another embodiment, a method of preparing a pharmaceutical composition comprises the step of: admixing an antibody with one or more pharmaceutically-acceptable carriers, wherein the antibody is a monoclonal antibody that was obtained from a transformed B cell or a cultured plasma cell of the invention.

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As an alternative to delivering antibodies or B cells for therapeutic purposes, it is possible to deliver nucleic acid (typically DNA) that encodes the antibody or the peptide/protein to a subject, such that the nucleic acid can be expressed in the subject *in situ* to provide a desired therapeutic effect. Suitable gene therapy and nucleic acid delivery vectors are known in the

30 art.

Pharmaceutical compositions may include an antimicrobial particularly if packaged in a multiple dose format. They may comprise detergent e.g., a Tween (polysorbate), such as Tween 80. Detergents are generally present at low levels e.g., less than 0.01%. Compositions may also include sodium salts (e.g., sodium chloride) to give tonicity. For example, a concentration of 10 ± 2 mg/ml NaCl is typical.

Further, pharmaceutical compositions may comprise a sugar alcohol (e.g., mannitol) or a disaccharide (e.g., sucrose or trehalose) e.g., at around 15-30 mg/ml (e.g., 25 mg/ml), particularly if they are to be lyophilized or if they include material which has been reconstituted from lyophilized material. The pH of a composition for lyophilization may be adjusted to between 5 and 8, or between 5.5 and 7, or around 6.1 prior to lyophilization.

The compositions of the invention may also comprise one or more immunoregulatory agents. In general, immunoregulatory agents include(s) an adjuvant. Accordingly, it is preferred, in particular for vaccines, that the pharmaceutical composition comprises an adjuvant. Examples of adjuvants include aluminum hydroxide (ALHYDROGEL®, available from Brenntag Biosector, Copenhagen, Denmark and AMPHOGEL®, Wyeth Laboratories, Madison, NJ), Freund's adjuvant, MPL™ (3-O-deacylated monophosphoryl lipid A; Corixa, Hamilton, IN), IL-12 (Genetics Institute, Cambridge, MA), TLR agonists (such as TLR-9 agonists), and QS-21 (a purified plant extract derived from the soap bark tree *Quillaja saponaria*).

As used herein, the term "adjuvant" refers in particular to a vehicle used to enhance antigenicity/immunogenicity. Adjuvants include a suspension of minerals (alum, aluminum hydroxide, or phosphate) on which the antigen is adsorbed; or water-in-oil emulsion, for example, in which antigen solution is emulsified in mineral oil (Freund incomplete adjuvant), sometimes with the inclusion of killed mycobacteria (Freund's complete adjuvant) to further enhance antigenicity (inhibits degradation of antigen and/or causes influx of macrophages). Immunostimulatory oligonucleotides (such as those including a CpG motif) can also be used as adjuvants. Adjuvants include biological molecules (a "biological adjuvant"), such as costimulatory molecules. Exemplary adjuvants include IL-2, RANTES, GM-CSF, TNF- α , IFN- γ , G-CSF, LFA-3, CD72, B7-1, B7-2, OX-40L, 4-1BBL and toll-like receptor (TLR) agonists,

such as TLR-9 agonists. The person of ordinary skill in the art is familiar with adjuvants (see, e.g., Singh (ed.) Vaccine Adjuvants and Delivery Systems. Wiley-Interscience, 2007), for example, those that can be included in a pharmaceutical composition. Preferably, the adjuvant is selected to elicit a Th1 immune response in a subject administered the pharmaceutical composition. In other words, the adjuvant comprised by the pharmaceutical composition preferably promotes a Th1 immune response. Preferably, the adjuvant is alum, an oil-in water composition, MF59, AS01, AS03, AS04, MPL, QS21, a CpG oligonucleotide, a TLR7 agonist, a TLR4 agonist, a TLR3 agonist, or a combination of two or more thereof.

- 10 The adjuvant may be selected from the group comprising mineral salts, surface-active agents, microparticles, cytokines, hormones, antigen constructs, polyanions, polyacrylics, or water-in-oil emulsions. Accordingly, the inventive composition may comprise one more adjuvants, e.g. one, two, three, four, five, six, seven, eight, nine, or ten or more adjuvants. For example the inventive composition may comprise one, two, three, four, five, six, seven, eight, nine, or
- 15 ten or more adjuvants selected from aluminum ("Alum"), aluminum hydroxide, aluminum phosphate, calcium phosphate, nonionic block polymer surfactants, virosomes, saponin (QS-21), meningococcal outer membrane proteins (Proteosomes), immune stimulating complexes (ISCOMs), Cochleates Dimethyl dioctadecyl ammonium bromide (DDA), Avridine (CP20,961), vitamin A, vitamin E, cell wall skeleton of *Mycobacterium phlei* (Detox®),
- 20 muramyl dipeptides and tripeptides, Threonyl MDP (SAF-1), Butyl-ester MDP (Murabutide®), Dipalmitoyl phosphatidylethanolamine MTP, Monophosphoryl lipid A, *Klebsiella pneumonia* glycoprotein, *Bordetella pertussis*, *Bacillus Calmette-Guérin*, *Vibrio cholerae* and *Escherichia coli* heat labile enterotoxin, trehalose dimycolate, CpG oligodeoxynucleotides, interleukin-2, interferon- γ , interferon- β , granulocyte-macrophage colony stimulating factor,
- 25 dehydroepiandrosterone, Flt3 ligand, 1,25-dihydroxy vitamin D3, interleukin-1, interleukin-6, interleukin-12, human growth hormone, 2-microglobulin, lymphotactin, polyanions, e.g. dextran, double-stranded polynucleotides, polyacrylics, e.g. polymethylmethacrylate, acrylic acid crosslinked with allyl sucrose (Carbopol 934P), or e.g. N-acetyl-glucosamine-3-yl-acetyl-L-alanyl-D-isoglutamine (CGP-11637), gamma inulin + aluminum hydroxide (Algamulin),
- 30 human dendritic cells, lysophosphatidyl glycerol, stearyl tyrosine, tripalmitoyl pentapeptide, Carbopol 974P NF polymer, water-in-oil emulsions, mineral oil (Freund's incomplete), vegetable oil (peanut oil), squalene and squalane, oil-in-water emulsions, Squalene + Tween-

80 + Span 85 (MF59), or e.g. liposomes, or e.g. biodegradable polymer microspheres, lactide and glycolide, polyphosphazenes, beta-glucan, or e.g. proteinoids. A list of typically used vaccine adjuvants may also be found in "Vaccine Adjuvants", edited by D.T. O'Hogan, Humana Press 2000. The adjuvant comprised in the inventive composition may also include

5 e.g. a synthetic derivative of lipid A, some of which are TLR-4 agonists, and include, but are not limited to: OM174 (2-deoxy-6-o-[2-deoxy-2-[(R)-3-dodecanoyloxytetra-decanoylamino]-4-o-phosphono-D-D-glucopyranosyl]-2-[(R)-3-hydroxy-tetradecanoylamino]-p-D-glucopyranosyldihydrogen-phosphate), (WO 95/14026) OM-294-DP (3S, 9R)-3-[(R)-dodecanoyloxytetradecanoylam, [(R)-3-hydroxytetradecanoylamino]decan-1,10-diol, 1,10-

10 bis(dihydrogenophosphate) (WO 99/64301 and WO 00/0462) OM 197 MP-Ac DP(3S,9R)-3-D(R)-dodecanoyl-oxytetradecanoylamino]-4-oxo-5-aza-9-[(R)-3-hydroxytetradecanoylamino]decan-1,10-diol,1-dihydrogenophosphate-10-(6-aminohexanoate) (WO 01/46127). For example the inventive vaccine may comprise only one of the above adjuvants, or e.g. two of the above adjuvants, e.g. combination adjuvants such as e.g. Alum and MPL,

15 or oil-in-water emulsion and MPL and QS-21, or liposomes and MPL and QS21.

It is preferred that the vaccine according to the invention comprises an adjuvant selected from the group comprising Alum, Ribi (Monophosphoryl lipid A, MPL), or MF59. Accordingly, the inventive vaccine composition may comprise Alum, or Ribi (Monophosphoryl lipid A, MPL),

20 or MF59, or e.g. Alum and Ribi, or e.g. Alum and MF59, or e.g. Ribi and MF59.

A particularly preferred adjuvant is a non-toxic bacterial lipopolysaccharide derivative. A preferred example of a suitable nontoxic derivative of lipid A, is monophosphoryl lipid A (MPL), or, more particularly, 3-Deacylated monophosphoryl lipid A (3DMPL). See, for

25 example, U.S. Pat. Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094. MPL primarily promotes CD4+ T cell responses with an IFN- γ (Th1) phenotype. In the pharmaceutical composition, for example small particle 3D-MPL can be used. Small particle 3D-MPL has a particle size such that it can be sterile-filtered through a 0.22 μ m filter. Such preparations are described in WO 94/21292. Alternatively, the lipopolysaccharide can be a B(1-6)

30 glucosamine disaccharide, as described in U.S. Pat. No. 6,005,099 and EP Patent No. 0 729 473 B1. One of skill in the art would be readily able to produce various lipopolysaccharides, such as 3D-MPL, based on the teachings of these references.

In addition to the aforementioned immunostimulants (that are similar in structure to that of LPS or MPL or 3D-MPL), acylated monosaccharide and disaccharide derivatives that are a sub-portion to the above structure of MPL are also suitable adjuvants.

5 Another particularly preferred adjuvant that can be used in the pharmaceutical composition is a saponin, such as QS21. QS-21 is a one of the active fractions derived from the soap bark tree *Quillaja saponaria* (Zhu W. and Tuo W., 2016, Nat Prod Chem Res 3(4): e113. QS-21: A potent vaccine adjuvant). QS denotes its source as *Q. saponaria* and the number 21 as the identity of the RP-HPLC peak. QS-21 is an acylated 3, 28-bisdesmodic triterpene glycosides
10 (1,3) or "saponin" with a molecular formula of $C_{92}O_{46}H_{148}$ and molecular weight of 1990 Da. Saponins, such as QS-21, may be preferably used as an adjuvant, e.g., for systemic administration. Use of saponins (e.g., use of Quil A, derived from the bark of the South American tree *Quillaja Saponaria* Molina) as adjuvants is familiar to the person of ordinary skill in the art (see, e.g., US 5,057,540 and EP 0 362 279 B1. EP 0 109 942 B1; WO 96/11711;
15 WO 96/33739). The haemolytic saponins QS21 and QS17 (HPLC purified fractions of Quil A) have been described as potent systemic adjuvants, and the method of their production is disclosed in U.S. Pat. No. 5,057,540 and EP 0 362279 B1.

Preferably, the pharmaceutical composition comprises monophosphoryl lipid A (MPL) and/or
20 a saponin, such as QS-21.

It is also preferred that a Toll-like receptor (TLR) agonist is used as an adjuvant. For example, the pharmaceutical composition may comprise a TLR agonist. For example, the TLR agonist can be a TLR-4 agonist such as a synthetic derivative of lipid A (see, e.g., WO 95/14026, and
25 WO 01/46127) an alkyl Glucosaminide phosphate (AGP; see, e.g., WO 98/50399 or U.S. Pat. No. 6,303,347; 6,764,840). Other suitable TLR-4 ligands, capable of causing a signaling response through TLR-4 are, for example, lipopolysaccharide from gram-negative bacteria and its derivatives, or fragments thereof, in particular a non-toxic derivative of LPS (such as MPL). Other suitable TLR agonists are: heat shock protein (HSP) 10, 60, 65, 70, 75 or 90;
30 surfactant Protein A, hyaluronan oligosaccharides, heparin sulphate fragments, fibronectin fragments, fibrinogen peptides and B-defensin-2, and muramyl dipeptide (MDP). For

example, the TLR agonist may be HSP 60, 70 or 90. Other suitable TLR-4 ligands are as described in WO 2003/011223 and in WO 2003/099195.

Additional TLR agonists (such as an agent that is capable of causing a signaling response through a TLR signaling pathway) are also useful as adjuvants, such as agonists for TLR2, TLR3, TLR7, TLR8 and/or TLR9. Accordingly, the composition may further include an adjuvant which is selected from the group consisting of: a TLR-1 agonist, a TLR-2 agonist, TLR-3 agonist, a TLR-4 agonist, TLR-5 agonist, a TLR-6 agonist, TLR-7 agonist, a TLR-8 agonist, TLR-9 agonist, or a combination thereof. For example, a TLR agonist may be used that is capable of causing a signaling response through TLR-1, for example one or more of from: tri-acylated lipopeptides (LPs); phenol-soluble modulin; *Mycobacterium tuberculosis* LP; S-(2,3-bis(palmitoyloxy)-(2-RS)-propyl)-N-palmitoyl-(R)-Cys-(S)-Ser-(S)-L-ys(4)-OH, trihydrochloride (Pam3Cys) LP which mimics the acetylated amino terminus of a bacterial lipoprotein and OspA LP from *Borrelia burgdorferi*. For example, a TLR agonist may be used that is capable of causing a signaling response through TLR-2, such as one or more of a lipoprotein, a peptidoglycan, a bacterial lipopeptide from *M. tuberculosis*, *B. burgdorferi* or *T. pallidum*; peptidoglycans from species including *Staphylococcus aureus*; lipoteichoic acids, mannuronic acids, Neisseria porins, bacterial fimbriae, Yersinia virulence factors, CMV virions, measles haemagglutinin, and zymosan from yeast. Furthermore, a TLR agonist may be used that is capable of causing a signaling response through TLR-3, such as one or more of double stranded RNA (dsRNA), or polyinosinicpolycytidylic acid (Poly IC), a molecular nucleic acid pattern associated with viral infection. Moreover, a TLR agonist may be used that is capable of causing a signaling response through TLR-5, such as bacterial flagellin. Also, a TLR agonist may be used that is capable of causing a signaling response through TLR-6, such as one or more of mycobacterial lipoprotein, di-acylated LP, and phenol-soluble modulin. Additional TLR6 agonists are described in WO 2003/043572. For example, a TLR agonist is used that is capable of causing a signaling response through TLR-7, such as one or more of a single stranded RNA (ssRNA), loxoribine, a guanosine analogue at positions N7 and C5, or an imidazoquinoline compound, or derivative thereof. In one embodiment, the TLR agonist may be imiquimod. Further TLR-7 agonists are described in WO 2002/085905. Moreover, a TLR agonist may be used that is capable of causing a signaling response through TLR-8. Suitably, the TLR agonist capable of causing a signaling response through TLR-8 is a

single stranded RNA (ssRNA), an imidazoquinoline molecule with anti-viral activity, for example resiquimod (R848); resiquimod is also capable of recognition by TLR-7. Other TLR-8 agonists which can be used include those described in WO 2004/071459. Furthermore, an adjuvant may include a TLR agonist capable of inducing a signaling response through TLR-9.

5 For example, the adjuvant can include HSP90, bacterial or viral DNA, and/or DNA containing unmethylated CpG nucleotides (e.g., a CpG oligonucleotide). For example, CpG-containing oligonucleotides induces a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 95/26204, WO 96/02555, WO 99/33488 and U.S. Pat. Nos. 5,278,302, 5,666,153, and 6,008,200 and 5,856,462. Accordingly,
10 oligonucleotides for use as adjuvants in the disclosed compositions include CpG containing oligonucleotides, for example, containing two or more dinucleotide CpG motifs. Also included are oligonucleotides with mixed internucleotide linkages.

The adjuvant can also include mineral salts such as an aluminum or calcium salts, in
15 particular aluminum hydroxide, aluminum phosphate and calcium phosphate.

Combinations of different adjuvants can also be used in the pharmaceutical compositions described herein. For example, as already noted, QS21 can be formulated together with (3D-)MPL. The ratio of QS21 : (3D-)MPL will typically be in the order of 1 : 10 to 10 : 1; such as
20 1 : 5 to 5 : 1, and often substantially 1 : 1. Typically, the ratio is in the range of 2.5 : 1 to 1 : 1 (3D-)MPL : QS21 (such as AS01 (GlaxoSmithKline)). Another combination adjuvant formulation includes (3D-)MPL and an aluminum salt, such as aluminum hydroxide (such as AS04 (GlaxoSmithKline)). When formulated in combination, this combination can enhance an antigen-specific Th1 immune response. The adjuvant formulation may comprise a mineral
25 salt, such as a calcium or aluminum (alum) salt, for example calcium phosphate, aluminum phosphate or aluminum hydroxide. Moreover, the adjuvant may include an oil and water emulsion, e.g., an oil-in-water emulsion (such as MF59 (Novartis) or AS03 (GlaxoSmithKline)). One example of an oil-in-water emulsion comprises a metabolisable oil, such as squalene, a tocol such as a tocopherol, e.g., alpha-tocopherol, and a surfactant, such
30 as sorbitan trioleate (Span 85) or polyoxyethylene sorbitan monooleate (Tween 80), in an aqueous carrier.

Moreover, the pharmaceutical composition, in particular the vaccine, according to the present invention preferably also comprises further component, such as a peptide or a protein, which may aggregate with the peptide/protein according to the present inventions to form aggregates, such as particles. An example of such a component is HBsAg or a fragment thereof as described herein. Accordingly, HBsAg or a fragment thereof as described herein may be (i) comprised by a (fusion) protein according to the present invention, and/or (ii) present in a pharmaceutical composition according to the present invention ("free" HBsAg), wherein the (fusion) protein may aggregate with the "free" HBsAg to form particles.

Medical Treatments, Kits and Uses

Medical treatments

In a further aspect, the present invention provides the use of

- (i) the peptide according to the present invention;
- (ii) the protein according to the present invention;
- (iii) the nucleic acid encoding the protein or the peptide according to the present invention;
- (iv) the virus-like particle according to the present invention;
- (v) the protein nanoparticle according to the present invention;
- (vi) the antibody, or the antibody fragment thereof, according to the present invention;
- (vii) the nucleic acid encoding the antibody, or antibody fragments according to the present invention;
- (viii) the vector comprising the nucleic acid according to the present invention;
- (ix) the cell expressing the antibody or the peptide according to the present invention, or comprising the vector according to the present invention; and/or
- (x) the pharmaceutical composition according to the present invention as a medicament.

Preferably

- (i) the peptide according to the present invention;

- (ii) the protein according to the present invention;
 - (iii) the nucleic acid encoding the protein or the peptide according to the present invention;
 - (iv) the virus-like particle according to the present invention;
 - 5 (v) the protein nanoparticle according to the present invention;
 - (vi) the antibody, or the antibody fragment thereof, according to the present invention;
 - (vii) the nucleic acid encoding the antibody, or antibody fragments according to the present invention;
 - (viii) the vector comprising the nucleic acid according to the present invention;
 - 10 (ix) the cell expressing the antibody or the peptide according to the present invention, or comprising the vector according to the present invention; and/or
 - (x) the pharmaceutical composition according to the present invention
- are for use in the prevention and/or treatment of malaria.

15 In other words, the antibody, or an antigen binding fragment thereof, according to the present invention is preferably for use in the prevention and/or treatment of malaria. It is also preferred that the peptide and/or the protein according to the present invention is for use in the prevention and/or treatment of malaria. Most preferably, the pharmaceutical composition according to the present invention as described above is for use in the prevention and/or

20 treatment of malaria.

Preferably, the malaria to be prevented and/or treated is caused by *P. falciparum* (infection).

Prevention of malaria refers in particular to prophylactic settings, wherein the subject was not

25 diagnosed with malaria (either no diagnosis was performed or diagnosis results were negative) and/or the subject does not show symptoms of malaria. Preferably, the inventive product is administered before infection, e.g. with *P. falciparum*. However, prevention of malaria also includes "post-exposure prophylaxis" (PEP), i.e. preventive treatment after a possible *P. falciparum* infection, for example after a mosquito bite in a *P. falciparum* affected area.

30 Prevention of malaria is in particular useful in high-risk subjects, such as in subjects staying in malaria areas (such as subjects living in malaria affected areas or travelling to malaria affected areas).

Accordingly, the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention is preferably used for prevention of malaria in subjects not diagnosed with malaria or in subjects showing no symptoms of malaria.

- 10 In therapeutic settings, in contrast, the subject is typically diagnosed with malaria and/or showing symptoms of malaria. Of note, the terms "treatment" and "therapy"/"therapeutic" of malaria include (complete) cure as well as attenuation of malaria.

- 15 Accordingly, the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention is preferably used for treatment of malaria in subjects diagnosed with malaria or in subjects showing symptoms of malaria.

- 25 It is also preferred that the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention is used for prevention and/or treatment of malaria in asymptomatic subjects. Those subjects may be diagnosed or not diagnosed with malaria.

Preferably, the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention is used for prevention of malaria, wherein the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention is administered up to three months before (a possible) Plasmodium infection, preferably up to one month before (a possible) Plasmodium infection, more preferably up to two weeks before (a possible) Plasmodium infection, even more preferably up to one week before (a possible) Plasmodium infection, and most preferably up to one day before (a possible) Plasmodium infection. Such a treatment schedule refers in particular to a prophylactic setting.

In general, the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention may be administered once or repeatedly. Accordingly, after the first administration of the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention, one or more subsequent administrations may follow, preferably a single dose per day or per every second day for 1, 2, 3, 4, 5, 6, 7, 8, 9,

10, 11, 12, 13, 1, 15, 16, 17, 18, 19, 20, or 21 days. It is also preferred that after the first administration of the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention, one or more subsequent administrations may follow, preferably a single dose once or twice per week for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 1, 15, 16, 17, 18, 19, 20, or 21 weeks. It is also preferred that after the first administration of the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention, one or more subsequent administrations may follow, preferably a single dose every 2 or 4 weeks for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 1, 15, 16, 17, 18, 19, 20, or 21 weeks. It is also preferred that after the first administration of the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention, one or more subsequent administrations may follow, preferably a single dose every two or four months for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 1, 15, 16, 17, 18, 19, 20, or 21 months. It is also preferred that after the first administration of the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention, one or more

subsequent administrations may follow, preferably a single dose once or twice per year for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years.

5 Preferably, the peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the pharmaceutical composition according to the present invention is
10 administered at a (single) dose of 0.005 to 100 mg/kg bodyweight, preferably at a (single) dose of 0.0075 to 50 mg/kg bodyweight, more preferably at a (single) dose of 0.01 to 10 mg/kg bodyweight, even more preferably at a (single) dose of 0.05 to 5 mg/kg bodyweight, and particularly preferably at a (single) dose of 0.1 to 1 mg/kg bodyweight.

15 The peptide according to the present invention, the protein according to the present invention, the virus-like particle according to the present invention, the protein nanoparticle according to the present invention, the antibody, or an antigen binding fragment thereof, according to the present invention, the nucleic acid according to the present invention, the vector according to the present invention, the cell according to the present invention or the
20 pharmaceutical composition according to the present invention may be administered by any number of routes such as oral, intravenous, intramuscular, intra-arterial, intramedullary, intraperitoneal, intrathecal, intraventricular, transdermal, transcutaneous, topical, subcutaneous, intranasal, enteral, sublingual, intravaginal or rectal routes. Intravenous administration, or subcutaneous administration or intramuscular administration are preferred
25 and intravenous administration or subcutaneous administration are more preferred.

Accordingly, the present invention also provides a method of preventing and/or treating malaria in a subject, wherein the method comprises administering to a subject in need thereof

- i) the peptide according to the present invention;
- 30 (ii) the protein according to the present invention;
- (iii) the nucleic acid encoding the protein or the peptide according to the present invention;

- (iv) the virus-like particle according to the present invention;
 - (v) the protein nanoparticle according to the present invention;
 - (vi) the antibody, or the antibody fragment thereof, according to the present invention;
 - (vii) the nucleic acid encoding the antibody, or antibody fragments according to the
5 present invention;
 - (viii) the vector comprising the nucleic acid according to the present invention;
 - (ix) the cell expressing the antibody or the peptide according to the present invention, or
comprising the vector according to the present invention; and/or
 - (x) the pharmaceutical composition according to the present invention.
- 10 Preferred embodiments of this method correspond to preferred embodiments of the medical
use as described above.

Further Use and Kits

- 15 In a further aspect, the present invention also provides the use of the antibody, or the antibody
fragment thereof, according to the present invention or of the pharmaceutical composition
according to the present invention for monitoring the quality of an anti-malaria vaccine by
checking that the antigen of said vaccine contains the specific epitope in the correct
conformation. Preferred antigens comprised by such an anti-malaria vaccine to be checked
20 include the peptide according to the present invention as described above.

Moreover, the present invention also provides the use of

- (i) the peptide according to the present invention;
- (ii) the protein according to the present invention;
- 25 (iii) the nucleic acid encoding the protein or the peptide according to the present
invention;
- (iv) the virus-like particle according to the present invention;
- (v) the protein nanoparticle according to the present invention;
- (vi) the antibody, or the antibody fragment thereof, according to the present invention;
- 30 (vii) the nucleic acid encoding the antibody, or antibody fragments according to the
present invention;
- (viii) the vector comprising the nucleic acid according to the present invention;

- (ix) the cell expressing the antibody or the peptide according to the present invention, or comprising the vector according to the present invention; and/or
 - (x) the pharmaceutical composition according to the present invention
- in diagnosis of malaria infection.

5

In addition also the use of

- (i) the peptide according to the present invention;
 - (ii) the protein according to the present invention;
 - (iii) the nucleic acid encoding the protein or the peptide according to the present
10 invention;
 - (iv) the virus-like particle according to the present invention;
 - (v) the protein nanoparticle according to the present invention;
 - (vi) the antibody, or the antibody fragment thereof, according to the present invention;
 - (vii) the nucleic acid encoding the antibody, or antibody fragments according to the
15 present invention;
 - (viii) the vector comprising the nucleic acid according to the present invention;
 - (ix) the cell expressing the antibody or the peptide according to the present invention, or comprising the vector according to the present invention; and/or
 - (x) the pharmaceutical composition according to the present invention
- 20 in determining whether an isolated blood sample (e.g., whole blood, serum and/or plasma) is infected with Plasmodium is provided.

Methods of diagnosis may include contacting the antibody or the peptide/protein according to the present invention with a sample. Such samples may be isolated from a subject, for
25 example an isolated tissue sample taken from, for example, nasal passages, sinus cavities, salivary glands, lung, liver, pancreas, kidney, ear, eye, placenta, alimentary tract, heart, ovaries, pituitary, adrenals, thyroid, brain, skin or blood, preferably plasma or serum. The methods of diagnosis may also include the detection of an antigen/antibody complex, in particular following the contacting of the antibody or the peptide/protein according to the
30 present invention with a sample. Such a detection step is typically performed at the bench, i.e. without any contact to the human or animal body. Examples of detection methods are

well-known to the person skilled in the art and include, e.g., ELISA (enzyme-linked immunosorbent assay).

In a further aspect, the present invention also provides a kit of parts comprising at least one
5 peptide according to the present invention, at least one protein according to the present
invention, at least one virus-like particle according to the present invention, at least one
protein nanoparticle according to the present invention, at least one pharmaceutical
composition according to the present invention, at least one antibody, or the antigen binding
fragment thereof, according to the present invention, at least one nucleic acid according to
10 the present invention, at least one vector according to the present invention, at least one cell
according to the present invention, and/or at least one pharmaceutical composition according
to the present invention. In addition, the kit may comprise a leaflet with instructions for
administration of the peptide according to the present invention, the protein according to the
present invention, the nucleic acid encoding the protein or the peptide according to the
15 present invention, the virus-like particle according to the present invention, the protein
nanoparticle according to the present invention, the antibody, or the antibody fragment
thereof, according to the present invention, the nucleic acid encoding the antibody, or
antibody fragments according to the present invention, the vector comprising the nucleic acid
according to the present invention, the cell expressing the antibody or the peptide according
20 to the present invention, or comprising the vector according to the present invention, and/or
the pharmaceutical composition according to the present invention and/or means for
administration of the peptide according to the present invention, the protein according to the
present invention, the nucleic acid encoding the protein or the peptide according to the
present invention, the virus-like particle according to the present invention, the protein
25 nanoparticle according to the present invention, the antibody, or the antibody fragment
thereof, according to the present invention, the nucleic acid encoding the antibody, or
antibody fragments according to the present invention, the vector comprising the nucleic acid
according to the present invention, the cell expressing the antibody or the peptide according
to the present invention, or comprising the vector according to the present invention, and/or
30 the pharmaceutical composition according to the present invention, such as a syringe or a
vessel.

BRIEF DESCRIPTION OF THE FIGURES

In the following a brief description of the appended figures will be given. The figures are intended to illustrate the present invention in more detail. However, they are not intended to limit the subject matter of the invention in any way.

Figure 1 shows for Example 1 exemplary staining of *P. falciparum* sporozoites by monoclonal antibodies MGG1, MGG2, MGG3, MGG4 and MGG8 (each of them based on VH/VL genes of antibodies isolated from Donor G) and by control antibody BKC3. The sporozoites were labeled with SYBR Green I and incubated with the monoclonal antibodies. Antibody detection was conducted with anti-human IgG conjugated to a fluorophore.

Figure 2 shows for Example 2 (A) a schematic overview over the assay used and (B) the inhibition of sporozoite traversal and invasion (ISTI) of hepatocytes by human monoclonal antibodies MGG1, MGG2, MGG3, MGG4, MGG8, MGH1, MGH2, MGH3 and for control antibody 2A10.

Figure 3 shows for Example 2 (A) a schematic overview over the experimental design of the *in vivo* humanized mouse model of sporozoite invasion and (B) the *in vivo* reduction of sporozoites by the selected antibodies MGG4, MGG8, MGH1, MGH2 and MGH3.

Figure 4 shows for Example 3 (A) a schematic overview over *P. falciparum* circumsporozoite protein. SP, signal peptide; RI, region I. (B) Sequence of PfCSP (isolate NF54, Uniprot accession number P19597; SEQ ID NO: 24). The functionally important region I is shown in bold. (C) Sequence of CSP peptides that were tested for binding by antibodies: 22-110-peptide (SEQ ID NO: 27), NPDP-peptide (SEQ ID NO: 23), and NANP-peptide (SEQ ID NO: 26). Amino acids belonging to region I are shown in bold.

Figure 5 shows for Example 3 the binding of monoclonal antibodies to different peptides by ELISA. Different dilutions of the antibodies were tested for binding to the CSP peptides (sequences are shown in Figure 4) and EC50 values were calculated for each antibody. The antibodies that were tested in the *in vivo* mouse model are boxed. The two antibodies that showed the best protection in this model (MGG4 and MGH2) showed good binding to the NPDP peptide and used VH3-30. All of the other antibodies that bound strongly to NPDP (with an EC50 <100ng/mL) also used VH3-30. One antibody, MGV3, bound relatively weakly to NPDP and 22-110 but not to the NANP repeat region.

Figure 6 shows for Example 4 the binding of monoclonal antibodies MGV3, MGG4, MGU5 and MGG1 to overlapping peptides from CSP. Only the region of CSP that showed binding by the monoclonal antibodies are shown.

Figure 7 shows for Example 5 the inhibition of binding of MGV3 by different monoclonal antibodies. Inhibition of binding is calculated by the median fluorescence intensity (FI) of IgG binding to sporozoites. MGU3 is an antibody that binds to the C-terminus of CSP, MGV3 binds to the NPDP region at the N-terminus, and the remaining antibodies bind to the repeat region of CSP.

Figure 8 shows for Example 6 the identification of antibodies binding to a C-terminal binding site in CSP. Briefly, C-terminal peptide 282 – 383 was coated at a concentration of 1 µg/mL, and the B cell supernatants were tested from a 1/3 dilution to a 1/648 dilution. MGU3 can bind to the peptide, while MGU1, MGU5 and MGU8 are shown as examples of antibodies that cannot bind to the peptide.

EXAMPLES

In the following, particular examples illustrating various embodiments and aspects of the invention are presented. However, the present invention shall not to be limited in scope by the specific embodiments described herein. The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. The present invention, however, is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only, and methods which are functionally equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those described herein will become readily apparent to those skilled in the art from the foregoing description, accompanying figures and the examples below. All such modifications fall within the scope of the appended claims.

Example 1: Isolation of human monoclonal antibodies that bind to *P. falciparum* sporozoites

Four Tanzanian donors (identified as donors G, H, U and V) who were protected from malaria challenge were selected for isolation of human monoclonal antibodies. To this end, peripheral blood mononuclear cells (PBMCs) were isolated from blood samples of the four donors. IgG memory B cells were isolated from frozen peripheral blood mononuclear cells (PBMCs) by magnetic cell sorting. The B cells were incubated with 0.5 µg/mL of anti-CD19-PECy7 antibodies for 20 min on ice and then incubated with mouse anti-PE microbeads for 30 min on ice. The cells were then stained with 3.75 µg/mL goat Alexa Fluor 647-conjugated anti-human IgG for 20 min on ice and sorted by FACS. As previously described in Traggiai et al. (2004) *Nat Med.* 10, 871-875, sorted B cells were immortalized with Epstein-Barr virus (EBV) and plated in single cell cultures in the presence of CpG and irradiated PBMC-feeder cells. After 14 days, culture supernatants were screened using a high-throughput flow cytometer for their capacity to stain sporozoites. In this assay, the sporozoites were labelled with 6.25x SYBR Green I and incubated with the B cell culture supernatants at a 1/2 dilution for 30 min at room temperature. Without any washing step, the sporozoites were then

incubated with 1 µg/mL of goat Alexa Fluor 647-conjugated anti-human IgG for 1 h at 4°C and analyzed by flow cytometry.

For sporozoite staining using recombinant monoclonal antibodies, the sporozoites were stained with 6.25x SYBR Green I and incubated with the monoclonal antibodies for 30 min at room temperature. The sporozoites were then washed once and stained with 2.5 µg/mL of goat Alexa Fluor 647-conjugated anti-human IgG for 30 min at room temperature and analyzed by flow cytometry.

An example of sporozoite staining is shown in Figure 1. Figure 1 shows exemplary staining of *P. falciparum* sporozoites by monoclonal antibodies MGG1, MGG2, MGG3, MGG4 and MGG5 (each of them based on VH/VL genes of antibodies isolated from Donor G) and by a negative control antibody.

Positive cultures were expanded and the VH and VL genes from individual clones were sequenced and cloned into human IgG1, Igκ and Igλ expression vectors (kindly provided by Michel Nussenzweig, Rockefeller University, New York, US) essentially as described (Tiller T, Meffre E, Yurasov S, Tsuiji M, Nussenzweig MC, Wardemann H (2008) Efficient generation of monoclonal antibodies from single human B cells by single cell RT-PCR and expression vector cloning. J Immunol Methods 329: 112-124) and expressed by transient transfection of Expi293F Cells using polyethylenimine (PEI).

Table 5 below shows exemplary human monoclonal antibodies that were found to bind to *P. falciparum* sporozoites, along with their VH and VL usage (see Tables 1 and 2 for SEQ ID NOs):

		Heavy chain		Light chain	
		VH	JH	VL	JL
Donor G	MGG1	VH3-20	JH6	VL1-51	JL3
	MGG2	VH3-74	JH5	VL7-46	JL2/JL3
	MGG3	VH3-30	JH2	VK2-29	JK1
	MGG4	VH3-30	JH3	VK4-1	JK4
	MGG8	VH3-73	JH5	VK2D-29	JK1

Donor H	MGH1	VH1-2	JH4	VK2-30	JK2
	MGH2	VH3-30	JH4	VK2-30	JK1
	MGH3	VH3-21	JH4	VK1-47	JK3
Donor U	MGU1	VH3-30	JH3	VL4-69	JL3
	MGU3	VH3-48	JH4	VK1-33	JK4
	MGU5	VH3-30	JH3	VK1-33	JK4
	MGU8	VH3-30	JH3	VK1-33	JK1/JK4
	MGU10	VH3-30	JH3	VL4-69	JL3
	MGU11	VH3-33	JH3	VK2-30	JK3
	MGU12	VH3-30	JH3	VK1-5	JK1
Donor V	MGV3	VH3-66	JH6	VK3-20	JK2

Example 2: Several monoclonal antibodies show potent *in vitro* and *in vivo* anti-sporozoite function

5

During the liver stage of the *Plasmodium* life cycle, sporozoites often traverse hepatocytes before productive invasion of target hepatocytes. Exemplary monoclonal antibodies MGG1, MGG2, MGG3, MGG4, MGG8, MGH1, MGH2 and MGH3 (see Tables 1 and 2 for SEQ ID NOs) were tested *in vitro* for their ability to inhibit sporozoite traversal and invasion of hepatocytes. To this end, a quantitative flow-cytometry-based assay was used, which is described in Kaushansky A, Rezakhani N, Mann H, Kappe SH, 2012: *Development of a quantitative flow cytometry-based assay to assess infection by Plasmodium falciparum sporozoites*. Mol Biochem Parasitol. 183(1):100-3. A schematic overview over this assay is shown in Figure 2A. Briefly, in this assay, the hepatocyte HC04 cell line was infected with *P. falciparum* sporozoites in the presence of FITC-dextran. Sporozoite traversal was measured by the uptake of FITC-dextran, which can enter hepatocytes with membranes injured during traversal. Sporozoite invasion was measured by staining of sporozoites in hepatocytes with an anti-circumsporozoite protein (anti-CSP) antibody. As a control, murine monoclonal antibody 2A10, which targets the NANP repeat region of the circumsporozoite protein (Zavala F. *et al.*, 1983, J. Exp. Med. 157: 1947 – 1957; Wirtz R.A. *et al.*, 1987, Bulletin of the World Health Organization 65(1): 39 – 45), was used.

10

15

20

Results are shown in Figure 2B. Here, the percentage of sporozoite invasion or traversal in the presence of a monoclonal antibody of interest relative to when irrelevant IgG is added is measured. A low percentage signifies good inhibition by the monoclonal antibody. In this assay, MGG4, MGH1, MGH2 and MGH3 showed the highest inhibition of sporozoite invasion. Hence, these antibodies, along with MGG8, were selected for further testing.

Selected monoclonal antibodies were then tested in the FRG huHEP liver-chimeric mouse model, essentially as described in Sack et al. (Sack et al., 2014, *Infection and Immunity* 82(2): 808-817. Model for in vivo assessment of humoral protection against malaria sporozoite challenge by passive transfer of monoclonal antibodies and immune serum) and, in particular, also in Vaughan et al. (Vaughan et al., 2012, *J Clin Invest* 122, 3618-3628. The FRG huHEP liver-chimeric mouse model measures sporozoite invasion and liver-stage parasite multiplication in mice with humanized livers). A schematic overview over the experimental design is shown in Figure 3A. In this model, the antibodies were first injected into mice, which were then infected by *P. falciparum* sporozoites by mosquito bite 16-24 h later. Liver parasite burden was then detected by imaging six days after infection.

Results are shown in Figure 3B. The liver burden in mice injected with a monoclonal antibody of interest was measured and calculated as a percentage of the liver burden in mice injected with non-specific IgG. The largest reduction of liver burden was observed in mice injected with antibody MGG4 or MGH2 (showing only 2.5% and 5.5% liver burden as compared to negative control mice, respectively).

Example 3: Potent monoclonal antibodies show distinct patterns of binding to CSP and use VH3-30

Plasmodium circumsporozoite protein (CSP) is an immunodominant protein that coats the entire sporozoite surface and that plays an important role in sporozoite function. As shown in Figure 4A, this protein contains an N-terminal segment starting with a signal peptide (SP) and ending with Region I (RI). Region I is a pentapeptide (KLKQP; SEQ ID NO: 25) that is involved in binding to hepatocytes and mosquito salivary glands. In CSP, region I is followed

by an NANP repeat region that is the immunodominant site for antibodies and a C-terminal thrombospondin-like domain that contains T cell epitopes (Figure 4A). Figure 4B shows an exemplary sequence of the circumsporozoite protein of *P. falciparum* isolate NF54 (SEQ ID NO: 24).

5

An antigen-agnostic approach as described in Example 1 was used to identify any antibody that can bind to the sporozoite surface. In that approach, it was found that all of the antibodies shown in Table 5 bound to CSP, confirming the immunodominance of this protein (data not shown).

10

Next, the binding of the antibodies to peptides from different parts of CSP as shown in Figure 4C was tested. In this assay, half-area 96-well ELISA plates were coated with whole recombinant CSP (SEQ ID NO: 24; 1 µg/mL), NANP-peptide (SEQ ID NO: 26; 2 µg/mL), NPDP-peptide (SEQ ID NO: 23; 5 µg/mL) or 22-110-peptide (SEQ ID NO: 27; 1 µg/mL) overnight at 4°C. The plates were blocked with 1% bovine serum albumin in PBS and incubated with titrated antibodies, followed by AP-conjugated goat anti-human IgG. The plates were then washed, substrate (p-NPP) is added and the plates were read at 405 nm.

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Results are shown in Figure 5 with the antibodies that were tested in the *in vivo* mouse model shown in a box. Interestingly, out of the five antibodies tested in the *in vivo* assay (MGG4, MGG8, MGH1, MGH2, MGH3), the two antibodies that showed the best function in the *in vivo* assay (MGG4, MGH2, see Example 2) bound well to the NPDP-peptide (SEQ ID NO: 23), i.e. in CSP at the junction between the N-terminus and the NANP repeat region. The other three antibodies tested in the *in vivo* assay (MGG8, MGH1, MGH3) showed only poor or negligible binding to this region. In contrast, the affinity of binding to a peptide containing only the repeat region or to whole CSP did not distinguish between the antibodies with different functional capacity in the *in vivo* assay.

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Interestingly, the CSP region to which the most potent antibodies MGG4 and MGH2 bind to, i.e. the junction between the N-terminus and the NANP repeat region, is not included in the leading malaria vaccine RTS,S. Rather, RTS,S incorporates the C-terminal half of the NANP repeat region and the C-terminal domain. The present data suggest that the junction between

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the N-terminus and the NANP repeat region is an important target of antibodies from protected individuals that show the most potent function in an *in vivo* model. Without being bound to any theory, the inventors assume that this region may be important due to its proximity to Region I, which is thought to be a target of parasite proteases that cleave the N-terminus of CSP during invasion of hepatocytes (Coppi et al. (2011) *J Exp Med* 208, 341-356; Coppi et al. (2005) *J Exp Med* 201, 27-33).

Further antibodies, which bound well to the NPDP-peptide (SEQ ID NO: 23) include MGG3, MGU5, MGU8 and MGU12.

Furthermore, all of the antibodies that bound well to the NPDP-peptide (MGG4, MGH2, MGG3, MGU5, MGU8 and MGU12) used VH3-30, suggesting that the usage of this VH is preferential for binding to this key region.

One antibody, MGV3, was found to bind relatively weakly to the NPDP-peptide and to the 22-110-peptide, but not to the NANP-peptide. This indicates that antibody MGV3 recognizes the N-terminus of CSP and the NPDP-region, but not to the NANP repeat region. Accordingly, MGV3 appears to bind slightly N-terminal as compared to the binding site of MGG4, MGH2, MGG3, MGU5, MGU8 and MGU12.

Other antibodies were found to bind well to the NANP-peptide, but weakly, if at all, to the NPDP-peptide and the 22-110-peptide, thereby indicating a binding site in the (middle of the) NANP-repeat region. Such antibodies include MGU11, MGU1, MGH3, MGH1, MGG8 and, to a lesser extent, MGG2 and MGG1.

Only antibody MGU3 showed no binding to any of the CSP-peptides used (22-110, NPDP-peptide, NANP-peptide), although it showed binding to the entire PfCSP. This may indicate a binding site for MGU3, which is located C-terminal of the NANP-repeat in CSP.

Example 4: Fine epitope mapping of monoclonal antibodies

To identify the precise region of CSP targeted by the monoclonal antibodies, linear epitope mappings of selected antibodies were performed against CSP (PEPperMAP® by PEPperPRINT GmbH, Heidelberg, Germany). To this end, antibodies MGV3, MGG4, MGU5 and MGG1 were tested for binding to an array of 15-aa CSP peptides (shifted by a single amino acid) covering the entire protein (Figure 6). Briefly, the sequence of circumsporozoite protein (CSP) was elongated by neutral GSGSGSG linkers (SEQ ID NO: 28) at the C- and N-terminus to avoid truncated peptides. The elongated antigen sequence was translated into linear 15 amino acid peptides with a peptide-peptide overlap of 14 amino acids (Figure 6). The resulting CSP peptide microarrays contained 457 different peptides printed in duplicate (914 peptide spots), additional custom control peptides (2 spots each control), c-Myc controls (2 spots) and a frame of HA control peptides (82 spots). The CSP peptide microarrays were incubated with the antibody samples at concentrations 1 µg/ml, 10 µg/ml and 100 µg/ml in incubation buffer followed by staining with secondary and control antibodies as well as read-out with a LI-COR Odyssey Imaging System. Quantification of spot intensities and peptide annotation were done with PepSlide® Analyzer.

Results are shown in Figure 6. It was found that MGV3, a peptide that recognizes the N-terminus and the NPDP peptide (Figure 5) but not the NANP repeat region, appears to bind to a NPDP motif, whereas MGG4 and MGU5 are able to bind to the first NANP repeat close to this region.

Example 5: Inhibition of binding of MGV3 to intact sporozoites

Next, it was tested whether monoclonal antibodies MGG1, MGG4, MGU5 and MGU3 could inhibit the binding of MGV3 to intact sporozoites in a blocking-of-binding (BOB) assay. In this assay, sporozoites were stained with 3.3x SYBR Green I and incubated with titrated monoclonal antibodies (from 0.1 to 100 µg/mL) for 20 min at room temperature. Without washing, the sporozoites were subsequently incubated with 10 µg/mL of biotin-labeled MGV3 for 20 min at room temperature. The sporozoites were washed twice, incubated with

streptavidin conjugated to Alexa Fluor 647 for 20 min at room temperature, and analyzed by flow cytometry. The decrease in median fluorescence intensity (median FI) in the Alexa Fluor 647 channel was used to measure the degree of inhibition of binding of biotinylated MGV3.

5 Results are shown in Figure 7. It was found that MGG4 and MGU5, which bind well to the NPDP peptide and could bind to the first NANP repeat based on the peptide array results (Figure 6), could inhibit binding by MGV3, while MGG1, which bound further away from the N-terminus, could not efficiently inhibit binding. This confirms the results of Examples 3 and 4 that antibodies binding to the NPDP-peptide, such as MGG4 and MGU5, bind to a more
10 N-terminal region of CSP than those antibodies, which do not bind to the NPDP-peptide, such as MGG1 or MGU3. In summary, the data suggest that antibodies binding to the NPDP-peptide, such as MGG4 and MGU5, have potent functional activity due to their ability to bind closer to the N-terminus.

15 As a note, unlabelled MGV3 could not inhibit binding as overall this antibody bound with low affinity to sporozoites and the concentration of biotinylated MGV3 used was much below its saturation point.

20 Example 6: Identification of antibodies binding to a C-terminal binding site in CSP

Since the data of Example 3 (Figure 5) suggest that of all antibodies tested only antibody MGU3 binds to a C-terminal binding site in CSP, different antibodies were tested for their ability to bind to the C-terminus of CSP.

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To this end, essentially the same experiment as described in Example 3 was performed with the antibodies shown in Table 1. However, instead of the CSP-test-peptides described in Example 3 (i.e., 22-110-peptide, NPDP-peptide, NANP-peptide) in the present experiment C-terminal peptide 282 – 383 (SEQ ID NO: 312) was used. Briefly, the C-terminal peptide 282
30 – 383 was coated at a concentration of 1 µg/ml, and the B cell supernatants were tested from a 1/3 dilution to a 1/648 dilution.

Results for selected antibodies MGU1, MGU3, MGU5 and MGU8 are shown in Figure 8 (data of the other antibodies of Table 1 not shown). As expected from the results of Examples 3 and 5, only antibody MGU3 bound to C-terminal peptide 282 – 383, whereas all other antibodies tested did not bind to the C-terminus of CSP. These results confirm that antibody MGU3 binds to the C-terminus of CSP, whereas the other antibodies do not bind to that region of CSP.

TABLE OF SEQUENCES AND SEQ ID NUMBERS (SEQUENCE LISTING):

SEQ ID NO	Sequence	Remarks
SEQ ID NO: 1	NPDP	CSP epitope
SEQ ID NO: 2	NPDPN	CSP epitope
SEQ ID NO: 3	NPDPNA	CSP epitope
SEQ ID NO: 4	NPDPNAN	CSP epitope
SEQ ID NO: 5	NPDPNANP	CSP epitope
SEQ ID NO: 6	NPDPNANPN	CSP epitope
SEQ ID NO: 7	GNPDPNANP	CSP epitope
SEQ ID NO: 8	GNPDPNANPN	CSP epitope
SEQ ID NO: 9	DGNPDPNANP	CSP epitope
SEQ ID NO: 10	NPDPNANPNK	CSP epitope
SEQ ID NO: 11	DGNPDPNANPN	CSP epitope
SEQ ID NO: 12	GNPDPNANPNK	CSP epitope
SEQ ID NO: 13	DGNPDPNANPNK	CSP epitope
SEQ ID NO: 14	ADGNPDPNANPN	CSP epitope
SEQ ID NO: 15	QPADGNPDPNANPNK	CSP epitope
SEQ ID NO: 16	ADGNPDPNANPNK	CSP epitope
SEQ ID NO: 17	PADGNPDPNANPNK	CSP epitope
SEQ ID NO: 18	ADGNPDPNANPNKN	CSP epitope
SEQ ID NO: 19	PADGNPDPNANPNKN	CSP epitope
SEQ ID NO: 20	QPADGNPDPNANPNKN	CSP epitope
SEQ ID NO: 21	PADGNPDPNANPNKNN	CSP epitope
SEQ ID NO: 22	QPADGNPDPNANPNKNN	CSP epitope
SEQ ID NO: 23	KQPADGNPDPNANPNKNN	NPDP-peptide
SEQ ID NO: 24	MMRKLAILSVSSFLFVEALFQEYQCYGSSNTRVL NELNYDNAGTNLYNELEMNYYGKQENWYSLK KNSRSLGENDDGNNEDNEKLRKPKHKKLKQPA DGNPDPNANPNVDPNANPNVDPNANPNVDP NANPNANPNANPNANPNANPNANPNANPNANP NPANPNANPNANPNANPNANPNANPNANPNANP NANPNANPNVDPNANPNANPNANPNANPNANP NPANPNANPNANPNANPNANPNANPNANPNANP NANPNANPNANPNANPNANPNANPNANPNKNNQ GNGQGHNMPNDPNRNVDENANANSVAKNN NNEEPSDKHIKEYLNKIQNSLSTEWSPCSVTCGN GIQVRIKPGSANKPKDEL DYANDIEKKICKMEKC SSVFNVVNSSIGLIMVLSFLN	PfCSP
SEQ ID NO: 25	KLKQP	CSP region I
SEQ ID NO: 26	NANPNANPNANPNANPNANPNANPNANPNANP NPANPNANP	NANP-peptide

SEQ ID NO: 27	EYQCYGSSSNTRVLNELNYDNAGTNLYNELEM NYYGKQENWYSLKKNRSRLGENDDGNNE KLRKPKHKKLKQPADGNPDPNANPNV	22-110-peptide
MGG1		
SEQ ID NO: 28	GFTFDDYA	CDRH1 aa
SEQ ID NO: 29	INWNGGST	CDRH2 aa
SEQ ID NO: 30	ARLGRAAREYYYYYMDV	CDRH3 aa
SEQ ID NO: 31	SSNIGNNY	CDRL1 aa
SEQ ID NO: 32	DNN	CDRL2 aa
SEQ ID NO: 33	LIYDNNKRP	CDRL2 long aa
SEQ ID NO: 34	GTWDSSLSAGV	CDRL3 aa
SEQ ID NO: 35	EVQLVESGGGVVVRPGGSLRLSCAASGFTFDDYA MSWVRQAPGKGLEWVSGINWNGGSTGYADS VKGRFTISRDNAKNSLYLQMNSLRAEDTALYHC ARLGRAAREYYYYYMDVWGKTTTVTVSS	VH aa
SEQ ID NO: 36	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYY SWYQQLPGTAPKLLIYDNNKRPSPGIPDRFSGSKS GTSATLGITGLQTGDEADYYCGTWDSSLSAGVF GGGTKLTVLGQ	VL aa
SEQ ID NO: 37	ggattcaccttgatgattatgcc	CDRH1 nuc
SEQ ID NO: 38	attaattggaatggtgtagcaca	CDRH2 nuc
SEQ ID NO: 39	gcgagactgggagagcagccgtgagtactactactacatg gacgtc	CDRH3 nuc
SEQ ID NO: 40	agctccaacattggaataattat	CDRL1 nuc
SEQ ID NO: 41	gacaataat	CDRL2 nuc
SEQ ID NO: 42	ctcatttatgacaataataagcgaccc	CDRL2 long nuc
SEQ ID NO: 43	ggcacatgggtagcagcctgagtgctggagtg	CDRL3 nuc
SEQ ID NO: 44	gagggtcagctggtggagtctgggggaggtgtggtacggcctgggg gggccctgagactctctgtgcagcctctggattcaccttgatgatta tgccatgagctgggtccgccaagctccagggaaggggctggagtg ggctctggtattaattggaatggtgtagcacaggttatgcagactct gtgaagggccgattcaccatctccagagacaacgccaagaactc cctgtatctgcaaatgaacagtctgagagccgaggacacggccttg tatcactgtgcgagactgggagagcagcccgtagtactactacta ctacatggacgtctggggcaaagggaccacggtcaccgtctcctc a	VH nuc

SEQ ID NO: 45	cagtctgtgtgacgcagccgcctcagtgctgcggccccaggac agaaggtcaccatctctgctctggaagcagctccaacattgggaa taattatgtatcctggtaccagcagctcccaggaacagccccaaa ctcctcattatgacaataataagcgaccctcagggttctgaccg attctctggctccaagtctggcacgtcagccaccctgggcatcacc ggactccagactggggacgaggccgattattactgcggcacatgg gatagcagcctgagtgctggagtgtcggcggagggaaccaagctg accgtcctaggtcag	VL nuc
MGG2		
SEQ ID NO: 46	GFTLNYYW	CDRH1 aa
SEQ ID NO: 47	INIDGSTT	CDRH2 aa
SEQ ID NO: 48	AKGSIKAGGFWSGYSNWFD	CDRH3 aa
SEQ ID NO: 49	PGPVTSGHY	CDRL1 aa
SEQ ID NO: 50	DTS	CDRL2 aa
SEQ ID NO: 51	LIYDTSNKH	CDRL2 long aa
SEQ ID NO: 52	LLSYGGAPV	CDRL3 aa
SEQ ID NO: 53	EVQLVESGGGLVQPGGSLRLSCAASGFTLNYY WMHWVRQAPGKGLVWVAHINIDGSTTTYADS VKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYC AKGSIKAGGFWSGYSNWFDPWGQGTLTVSS	VH aa
SEQ ID NO: 54	QAVVTQEPLSLTVSPGGTVTLTCDSDPGPVTSGH YPYWFQQKPGQVPRTLIYDTSNKHSWTPARFS GSLGGAALTLGAQPEDEADYYCLLSYGGAP VFGGGTKLTVL	VL aa
SEQ ID NO: 55	ggattcacctcaataactactgg	CDRH1 nuc
SEQ ID NO: 56	attaatatcgatggcagtactaca	CDRH2 nuc
SEQ ID NO: 57	gcaaagggaagtattaaggccggagggttttggagtgggtactccaa ctgggtcgacccc	CDRH3 nuc
SEQ ID NO: 58	cctggacctgtcaccagtgggtcattat	CDRL1 nuc
SEQ ID NO: 59	gataccagc	CDRL2 nuc
SEQ ID NO: 60	ctgatttatgataccagcaacaacac	CDRL2 long nuc
SEQ ID NO: 61	ctgctctcgatgggtgggtcccctgta	CDRL3 nuc

SEQ ID NO: 62	gaggtgcagctggtggagtcgggggaggcttagttcagccgggg gggtccctgagactctctgtgcagcctctggattcacctcaataa ctactggatgcactgggtccgccaagctccaggaaggggctggt ctgggtcgacatattaatatcgatggcagttactacaacctacgcgg actccgtgaagggccgattcacctctccagagacaacgccaag aacacgctgtatctgcaaatgaacagtctgagagccgaggacacg gctgtctattactgtgcaaggggaagtattaaggccggagggttttgg agtggttactccaactggttcgacccctggggccagggaaacctgg tcaccgtctcctcag	VH nuc
SEQ ID NO: 63	caggctgtgggtgactcaggagccctcactgactgtgtcccaggag ggacagtcactctcacctgtgactccgaccctggacctgtcaccag tggtcattatccctactggttcagcagaagcctggccaagtcccc aggacactgattatgataccagcaacaacactcctggacacctg cccggtttcaggctccctcctgggggcaaagctgccctgacctt tcgggtgcgcagcctgaggatgaggctgactattactgctgtctc gtatgggtgtgccctgtattcggcggagggaacaaactgaccgtc ctaa	VL nuc
MGG3		
SEQ ID NO: 64	GFTFSTFG	CDRH1 aa
SEQ ID NO: 65	IWYDGSSK	CDRH2 aa
SEQ ID NO: 66	VKVGANWGWRYFDL	CDRH3 aa
SEQ ID NO: 67	QSLHSDGNTY	CDRL1 aa
SEQ ID NO: 68	EVS	CDRL2 aa
SEQ ID NO: 69	LIYEVSSRF	CDRL2 long aa
SEQ ID NO: 70	MQGIHSWT	CDRL3 aa
SEQ ID NO: 71	QEQLVESGGGVVQPGKSLRLSCAASGFTFSTFG MHWVRQAPGKLEWVAVIWDGSSKYHADS VKGRFTISRDNSKSTLYLQMNSLRAEDTAMYYC VKVGANWGWRYFDLWGRGTLVTVSS	VH aa
SEQ ID NO: 72	DIVMTQTPLSLSVTPGQPASISCKSSQSLHSDG NTYLSWYLQKPGQSPQLLIYEVSSRFSGVPDRFS GSGSGTDFTLKISRVEADDVGVYYCMQGIHSW TFGQGTKVEIK	VL aa
SEQ ID NO: 73	gattcaccttcagttaccttggc	CDRH1 nuc
SEQ ID NO: 74	atctgggtatgatggaagtagtaaa	CDRH2 nuc
SEQ ID NO: 75	gtgaaagtcggagctaactggggatggagggtacttcgatctc	CDRH3 nuc
SEQ ID NO: 76	cagagcctcctacatagtgatggaacacctat	CDRL1 nuc
SEQ ID NO: 77	gaagttcc	CDRL2 nuc
SEQ ID NO: 78	ctgatctatgaagttccagccggttc	CDRL2 long nuc

SEQ ID NO: 79	atgcaaggcatacactcgtggacg	CDRL3 nuc
SEQ ID NO: 80	caggagcaactggaggagctgggggaggcgtggccagcctggg aagtcctgagactctcctgtgcagcctcggattcaccttcagtacc ttggcatgcactgggtccgccagggtccaggcaaggggctggagt gggtggcagtcactcgtgatgatggaagtagtaataacatgcagac tccgtgaagggccgattcaccatctccagagacaattccaagagc acgctgtatctgcaaatgaacagcctgagagctgaggacacggct atgtattactgtgtgaaagtcggagctaactggggatggaggtaattc gatctctggggccgtggcaccctggcaccgtctcctcag	VH nuc
SEQ ID NO: 81	gatattgtgatgaccagactccactctctgtccgtcaccctgg acagccggcctccatctcctgcaagtctagtcagagcctcctacat agtgatggaaacacctatttcttggtagctgcagaagccaggcc agtctccacagctcctgatctatgaagttccagccggttctctggag tgccagatagggtcagcggcagcgggtcaggacagattcacact gaaaatcagccgggtggaggctgacgatgttggggttactactgc atgcaaggcatacactcgtggacgttcggccaagggaaccaagggtg gaaatcaaac	VL nuc
MGG4		
SEQ ID NO: 82	GFRFSDYG	CDRH1 aa
SEQ ID NO: 83	IWYDGSNE	CDRH2 aa
SEQ ID NO: 84	AKLLVGITTDVFDV	CDRH3 aa
SEQ ID NO: 85	QSVLSSSNKNKY	CDRL1 aa
SEQ ID NO: 86	WAS	CDRL2 aa
SEQ ID NO: 87	LIYWASTRE	CDRL2 long aa
SEQ ID NO: 88	QQYYTASPF	CDRL3 aa
SEQ ID NO: 89	QVQLVESGGGVVQGRSLRLSCAASGFRFSDYG MHWVRQAPGKGLEWVALIWYDGSNESYLDV KGRFTISRDNKNTLYLQMNNLRTEDEVYYCA KLLVGITTDVFDVWVGQTVTVSS	VH aa
SEQ ID NO: 90	DIVMTQSPDSLAVSLGERATINCRSSQSVLSSSN NKNYLAWYQHKPRQPPKLLIYWASTRESGVPD RFGSGSGTDFLTISLQAEDVAVYYCQQYYTA SPFFGGGKVEIK	VL aa
SEQ ID NO: 91	ggattcaggttcagtactatggc	CDRH1 nuc
SEQ ID NO: 92	atatgggtatgatggaagtaataa	CDRH2 nuc
SEQ ID NO: 93	gcgaaactactagtggaataactactgatgttttgatgtc	CDRH3 nuc
SEQ ID NO: 94	cagagtgtttatccagctccaacaataagaactac	CDRL1 nuc
SEQ ID NO: 95	tgggcatct	CDRL2 nuc
SEQ ID NO: 96	ctcatttactgggcatctaccgggaa	CDRL2 long nuc

SEQ ID NO: 97	cagcaatattatactgcttccccatt	CDRL3 nuc
SEQ ID NO: 98	caggtgcagctggaggagctctgggggaggcgtgggtccagcctggg aggtccctgagactctcctgtgcagcctctggattcaggttcagtgac tatggcatgcactgggtccgccaggctccgggcaaggggctggag tgggtggcacttatatggatgatggaaagtaataatcctatttagact ccgtgaagggccgattcaccatctccagagacaattccaagaaca cactgtatctgcaaatgaacaacctgagaactgaggacacggctgt gtattactgtgcgaaactactagtggaattactactgatgttttgatgt ctggggccaagggacagtgggtaccgtctcttcag	VH nuc
SEQ ID NO: 99	gacatcgtgatgacctcagactccctggctgtgtctctggg cgagagggccaccatcaactgcaggtccagccagagtgtttatcc agctccaacaataagaactacttagcttggtaccagcacaaccca cgacagcctcctaaactgctcattactgggcatctaccgggaatc cgggtccctgaccgattcagtggcagcgggtctgggacagattc actctcaccatcagcagcctgcaggctgaagatgtggcagttatta ctgtcagcaatattatactgcttccccattttcggcggagggaacca ggtagagatcaaac	VL nuc
MGG8		
SEQ ID NO: 100	GFMISGSV	CDRH1 aa
SEQ ID NO: 101	IRDKANNEAT	CDRH2 aa
SEQ ID NO: 102	TRGIIVGDTWHFDP	CDRH3 aa
SEQ ID NO: 103	ESLLRSDGKTY	CDRL1 aa
SEQ ID NO: 104	EVS	CDRL2 aa
SEQ ID NO: 105	LMYEVSKRF	CDRL2 long aa
SEQ ID NO: 106	MQSIQLVT	CDRL3 aa
SEQ ID NO: 107	EVQLVESGGGLVQPGGSLKLSAASGFMISGSVL HWVRQASGKGLEWLGRIRDKANNEATAYAAASV KGRFTISRDDSKDTTYLQMNSLRIEDTAVYYCTR GIIVGDTWHFDPWGOGTLTVSS	VH aa
SEQ ID NO: 108	DIVMTQTPLSLSVTPGQTASISCKSSSLLRSDGK TYLYWYLQKPGQSPQLLMYEVSKRFSGVPRFS GSGSGTDFTLKISRVEDDDVGIYYCMQSIQLVTF GQGTEKVEIK	VL aa
SEQ ID NO: 109	gggttcagatcagtggtctctgtt	CDRH1 nuc
SEQ ID NO: 110	attagagacaagctaacaatgaggcgaca	CDRH2 nuc
SEQ ID NO: 111	acgaggggtatcatagtaggtgacacctggcacttcgacccc	CDRH3 nuc
SEQ ID NO: 112	gagagcctcctgagaagcgatggaaagacctta	CDRL1 nuc
SEQ ID NO: 113	gaagttcc	CDRL2 nuc
SEQ ID NO: 114	ctgatgtatgaagttccaagcgcttc	CDRL2 long nuc

SEQ ID NO: 115	atgcaaagtatacagcttgtagct	CDRL3 nuc
SEQ ID NO: 116	gaagtgcagctggaggagtcggggaggcctggccagcctggg gggtccctgaaactctcctgtgcagcctctgggttcagatcagtggc tctgttctacactgggtccgccaggcctccgggaaaggctggagt ggcttggccgtattagagacaaagctaacaatgaggcgacagcat atgcagcgtcgggtgaaaggcagggtcaccatctccagagatgattc aaaggacacgacatatctgcaaatgaacagcctgagaatcgagg acacggccgtgtattactgtacgaggggtatcatagtaggtgacacc tggcacttcgacccctggggccagggaaccctggtcaccgtctcct cag	VH nuc
SEQ ID NO: 117	gatattgtgatgaccagactccactctctgtccgtcaccctgg acagacggcctccatctcctgcaagtctagttagagcctcctgaga agcgatggaaagacctactgtattggatctgcagaagccaggcc agtctccacagctcctgatgtatgaagttccaagcctctctggag tgccagataggttcagtggcagcgggtcaggaacagattttact gaaaatcagccgggtggagactgatgatgttggcatttattactgat gcaaagtatacagcttgtagcttccggccaagggaaccaaggtggaa atcaaac	VL nuc
MGH1		
SEQ ID NO: 118	GYTFTDYY	CDRH1 aa
SEQ ID NO: 119	INPYIGVS	CDRH2 aa
SEQ ID NO: 120	AACSNVGCYVY	CDRH3 aa
SEQ ID NO: 121	QSLVYSDGNTY	CDRL1 aa
SEQ ID NO: 122	KVS	CDRL2 aa
SEQ ID NO: 123	LIYKVSNRD	CDRL2 long aa
SEQ ID NO: 124	MQGTHWPDT	CDRL3 aa
SEQ ID NO: 125	QVQLVQSGAEVKKPGASVRVSCKTSGYTFTDYY VHWVRQAPGHGLECMGWINPYIGVSKYAQKF QGRVTLTRDTSISTAYMEISRLTSDDTAVYYCAA CSNVGCYVYWGOGLTVSS	VH aa
SEQ ID NO: 126	DVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDG NTYLNWFQQRPGQSPRRLIYKVSNRDSGVPDR FSGSGSGTDFTLKISRVEAEDVAIYFCMQGTHW PDTFGQGTKLEIK	VL aa
SEQ ID NO: 127	ggatacacgttcaccgactactat	CDRH1 nuc
SEQ ID NO: 128	atcaatccttacattgggtgtctca	CDRH2 nuc
SEQ ID NO: 129	gcggctttagtaacgttggctgctacgtctat	CDRH3 nuc
SEQ ID NO: 130	caaagtctcgtgtacagtgtggaacacctac	CDRL1 nuc
SEQ ID NO: 131	aaggtttct	CDRL2 nuc

SEQ ID NO: 132	ctaattataaggtttctaatecgggac	CDRL2 long nuc
SEQ ID NO: 133	atgcaagggtacacactggcctgacact	CDRL3 nuc
SEQ ID NO: 134	cagggtgcagctggtgcagtcctggggctgagggaagaagcctggg gcctcagtgagagtcctgcaagacatctggatacacgttaccg actactatgtccactgggtgcagaggccccaggacacgggctg agtgcattgggctggatcaatccttacattgggtgtctcaaagtatgcac agaagttcagggcaggggtcaccttgaccagggtacacgtccatca gcacagcctacatggaaattagcaggctaacatctgacgacacgg ccgtctattactgtcggctttagtaacgttggctgctacgtctattgg ggccagggtacgctgggtcacctgtcctcag	VH nuc
SEQ ID NO: 135	gatgttgatgactcagtcctcctcctgcccgtcaccttgga cagccggcctccatctcctgcaggctagtcacaaagtctcgtgtaca gtgatggaaacacactactgaattgggttcagcagaggccaggcca atctccaaggcgcctaattataaggtttctaatecgggactctgggg cccagacagattcagcggcagtgaggctcaggcactgatttcacactg aaaatcagcaggggtggaggctgaggatgttcgatttattctgcatg caagggtacacactggcctgacactttggccaggggaccaaactg gagatcaaac	VL nuc
MGH2		
SEQ ID NO: 136	GFSFSSYA	CDRH1 aa
SEQ ID NO: 137	TRYDGSNK	CDRH2 aa
SEQ ID NO: 138	AKVGDGTVAGTIDY	CDRH3 aa
SEQ ID NO: 139	QSLVYSDGNTY	CDRL1 aa
SEQ ID NO: 140	KVS	CDRL2 aa
SEQ ID NO: 141	LIYKVSNRD	CDRL2 long aa
SEQ ID NO: 142	MQGTHWWT	CDRL3 aa
SEQ ID NO: 143	QVQLVESGGGVVQPGGSLRLSCTASGFSFSSYA MHWVRQAPGKGLEWVAYTRYDGSNKFYLDV QGRFTISRDNKNTLYLEMDSLRLEDTAVYFCAK VGDGTVAGTIDYWGOGTLTVSS	VH aa
SEQ ID NO: 144	YIVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGN TYLNWYQQRPGQSPRRLIYKVSNRDSGVPDRFS GSGSGTDFTLKISRVEAEDVGVYYCMQGTHW WTFGQGTKVEIK	VL aa
SEQ ID NO: 145	ggtttcagcttcagtagttatgcc	CDRH1 nuc
SEQ ID NO: 146	acacgggtatgatggaagtaataag	CDRH2 nuc
SEQ ID NO: 147	gcgaagtgggggacgggacagtggtggtactattgacta	CDRH3 nuc
SEQ ID NO: 148	caaagcctcgtatatagtgatggaacacctac	CDRL1 nuc
SEQ ID NO: 149	aaggtttct	CDRL2 nuc

SEQ ID NO: 150	ctaatttataagggttctaatacgggac	CDRL2 long nuc
SEQ ID NO: 151	atgcaagggtacacactgggtggacg	CDRL3 nuc
SEQ ID NO: 152	cagggtgcagctgggtgagctctgggggaggcgtgggtccagcctggg gggtccctgagactctcctgtacagcgtctgggttcagctcagtagtt atgccatgcactgggtccgccaggctccaggcaagggtgaggt gggtggcatatacacgggtatgatggaagtaataagttctacctagact ccgtgcagggtccgattcaccatctccagagacaattccaagaaca cgctgtatctggaaatggacagcctgagactgaggacacggctgt ctatttctgtcgaaagtgggggacgggacagtggtggtactattga ctactggggccagggaacgctgggtcaccgtctcctcag	VH nuc
SEQ ID NO: 153	tatattgtgatgactcagtcctcactctcctgcccgtcacccttgga cagccggcctccatctcctgcaggctctagtaaagcctcgtatata gtgatggaaacacactactgaattggtatcagcagaggccaggcca atctccaaggcgcctaatttataagggttctaatacgggactctgggt cccagacagatttagcggcagtggtgagcagcactgattcacactg aaaatcagcagggtggaggctgaggatgtggggtttattactgcat gcaagggtacacactgggtggacgttcggccaagggaaccaagggtg aatcaaac	VL nuc
MGH3		
SEQ ID NO: 154	GFTFSSYT	CDRH1 aa
SEQ ID NO: 155	ISSSGSYI	CDRH2 aa
SEQ ID NO: 156	ARNVLDSSGYPTYFDY	CDRH3 aa
SEQ ID NO: 157	QSLYSNGYNY	CDRL1 aa
SEQ ID NO: 158	LGS	CDRL2 aa
SEQ ID NO: 159	LIYLGSNRA	CDRL2 long aa
SEQ ID NO: 160	MQAVQTPLT	CDRL3 aa
SEQ ID NO: 161	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYTM NWVRQAPGKGLEWVSSISSSGSYIYYADSVKGR CTISRDNAKNSLDLQMNSLRAEDAAVYYCARN VLDSSGYPTYFDYWGGGTTLTVSS	VH aa
SEQ ID NO: 162	DIVMTQSPLSLPVTPGEPASISCRSSQSLYSNGY NYLDWYVQKPGQSPRLIYLGSNRASGVPRFS GSGSGTDFTLRISRVEAEDVGFYYCMQAVQTPL TFGGGTKVEIK	VL aa
SEQ ID NO: 163	ggattcaccttcagtagttatacc	CDRH1 nuc
SEQ ID NO: 164	attagtagtagtggttagttacata	CDRH2 nuc
SEQ ID NO: 165	gcaagaaatgtcttgacagtagtggttaccacgtactttgactat	CDRH3 nuc
SEQ ID NO: 166	agagcctcctatatagtaattggatacaactat	CDRL1 nuc
SEQ ID NO: 167	ttgggttct	CDRL2 nuc

SEQ ID NO: 168	ctgatctattgggttctaatacgggcc	CDRL2 long nuc
SEQ ID NO: 169	atgcaagctgtacaaactcccctcact	CDRL3 nuc
SEQ ID NO: 170	gagggtgcagctggaggagctctgggggaggcctgggtcaagcctggg gggtccctgagactctcctgtgcagcctctggattcaccttcagtagt tataccatgaactgggtccgccaggctccagggaaggggctggag tgggtctcatccattagtagtagtggttagttacatattacgcagact cagtgaagggccgatgcaccatctccagagacaacccaagaac tactggatctgcaaatgaacagcctgagagccgaggacgcggct gtgtattactgtgcaagaaatgtcttggacagtagtggttaccacacg tactttgactattggggccagggaacgctgggtaccgtctcctcag	VH nuc
SEQ ID NO: 171	gatattgtagtactcagtcctcactctccctgcccgtcacccctgg agagccggcctccatctcctgcaggcttagtcagagcctcctatat agtaatggatacaactatctggattggtacgtgcagaagccagggc agtctccacgcctcctgatctatttgggttctaatacgggcctccgggg tccctgacaggttcagtggtgagtcaggtcaggtcacagattttactg agaatcagcagagtgagggtgaggatgttgggtttattactgcatg caagctgtacaaactcccctcactttcggcgagggaaccaagggtg gagatcaaac	VL nuc
MGU1		
SEQ ID NO: 172	GFAFSSYG	CDRH1 aa
SEQ ID NO: 173	IWHDGTNK	CDRH2 aa
SEQ ID NO: 174	AIWYLDSPDHGFDI	CDRH3 aa
SEQ ID NO: 175	NGHSSNA	CDRL1 aa
SEQ ID NO: 176	VNSDGS	CDRL2 aa
SEQ ID NO: 177	QAWDSGIWV	CDRL3 aa
SEQ ID NO: 178	QVQLVESGGGVVQPGKSLRLSCAASGFAFSSYG MNWVRQAPGKGLEWVAVIWHHDGTNKKYRDS VKGRFISRDNAKNTLYLQMDSLAEEDTAMYYC AIWYLDSPDHGFDIWRGTMVTSS	VH aa
SEQ ID NO: 179	QLVLTQSPASASLGVSVTLTCTLNNGHSSNAIA WHQQQPGKGPRLMKVNSDGSNKGAAVP DRFSGSSSGTERHLTISSLQSDDEADYYCQAWD SGIWWFGGGTKLTVL	VL aa
SEQ ID NO: 180	ggattcgcttcagtagttatggc	CDRH1 nuc
SEQ ID NO: 181	atttggcatgatggcaccaataaa	CDRH2 nuc
SEQ ID NO: 182	gccatttgggtatcttgatagtcctgatcatggttcgatatc	CDRH3 nuc
SEQ ID NO: 183	aatggccacagttcaatgcc	CDRL1 nuc
SEQ ID NO: 184	gttaatagtgatggcagcca	CDRL2 nuc
SEQ ID NO: 185	caggcctgggacagtggttcatttgggtt	CDRL3 nuc

SEQ ID NO: 186	caggtgcagctggtggagtctgggggaggcgtggtccagcctggg aggtccctgagactctcatgtgcagcctccggattcgcttcagtagt tatggcatgaactgggtccgccaggctccaggcaagggaactggag tgggtggcagttatttggcatgatggcaccaataaatactatagagac tccgtgaagggccgattcatcatctccagagacaatgccaagaac accttgatctgcaaattggacagcctgagcgctgaggacacggcta tgtattactgtgccatttggatcttgatagctctgatcatggttcgatat ctggggccgagggaacaatggtcaccgtctcttcag	VH nuc
SEQ ID NO: 187	cagcttgctcgtactcaatcgccctctgctctgctccctgggagt ctcggtcaccctcacctgtactctgaacaatggccacagttccaat ggcatcgcatggcatcaacagcagccagggaaggccctcggtat ttgatgaagggttaatagtgatggcagccacaataagggggccgctg tccctgatcgcttctcaggctctagttctgggactgagcgccacctc accatctccagcctccagctctgacgataggctgactattattgtca ggcctgggacagtggttcatttgggttttcggcgagggaaccaagttg accgtcctag	VL nuc
MGU3		
SEQ ID NO: 188	GFTFSDYN	CDRH1 aa
SEQ ID NO: 189	ISHSSSTT	CDRH2 aa
SEQ ID NO: 190	ARLRPLSYSGRYRDY	CDRH3 aa
SEQ ID NO: 191	QDVSNY	CDRL1 aa
SEQ ID NO: 192	DAS	CDRL2 aa
SEQ ID NO: 193	LIYDASTLQ	CDRL2 long aa
SEQ ID NO: 194	QQYDSLPLT	CDRL3 aa
SEQ ID NO: 195	EVLLVESGGGLVQPGGSLRLSCAASGFTFSDYN MHWVRQAPGKGLEWLSYISHSSSTYYADSVR GRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR LRPLSYSGRYRDYWGQGTlVTVSS	VH aa
SEQ ID NO: 196	DIQMTQSPSSLSASVGDRTITCQASQDVSNYV NWYQQKPGKAPKVLIIYDASTLQTGVPSRFGSG SGTDFTFSSISLQPEDATYYCQQYDSLPLTFGGG TKVEIK	VL aa
SEQ ID NO: 197	ggattcaccttcagtactataac	CDRH1 nuc
SEQ ID NO: 198	attagtcatagtagtagtaccaca	CDRH2 nuc
SEQ ID NO: 199	gcgagacttcgtcccttatcgtatagtggcaggtagccgcgactac	CDRH3 nuc
SEQ ID NO: 200	caggacgttagtaattat	CDRL1 nuc
SEQ ID NO: 201	gatgcatcc	CDRL2 nuc
SEQ ID NO: 202	ctgatctacgatgcatccactttgcaa	CDRL2 long nuc
SEQ ID NO: 203	cagcagtatgatagcctccactcact	CDRL3 nuc

SEQ ID NO: 204	gaggtgctactagtggagctctgggggaggcttggtacaacctgggg ggccctgagactctctgtgcagcctctggattcaccttcagtact ataacatgcactgggtccgccaggctccagggaaggggctggagt ggctttcatacattagtcatagtagtagtaccacatactacgcagact ctgtgaggggcccattcacatctccagagacaatgccaagaact cactgtatctgcaaatgaacagcctgagagccgaggacacggctg tgtattactgtgcgagacttcgtcccttatctatagtggcaggtagccg cgactactggggccagggaacgctggcaccgtctcctcag	VH nuc
SEQ ID NO: 205	gacatccagatgaccagtcctcatcctcctgtctgcatctgtagg agacagagtcacatcacttgccaggcgagtcaggacgtagtaatt tatgtaaattggatcagcagaaaccagggaagcccctaagggtcc tgatctacgatgcattcttgaacagggtcccatcaagggttc agtggagtgatcggggacagattttactttcagcatcagcagcct gcagcctgaagatattgcaacatattactgtcagcagtagtagcc tcccactcacttcggcgaggaggaccaagggtggagatcaaac	VL nuc
MGU5		
SEQ ID NO: 206	GFSFSSYG	CDRH1 aa
SEQ ID NO: 207	IWHDGTNK	CDRH2 aa
SEQ ID NO: 208	TKRAGWGDALDI	CDRH3 aa
SEQ ID NO: 209	QDISNY	CDRL1 aa
SEQ ID NO: 210	DAS	CDRL2 aa
SEQ ID NO: 211	LIYDASNLE	CDRL2 long aa
SEQ ID NO: 212	QQQRI	CDRL3 aa
SEQ ID NO: 213	QVQLVESGGGVVQPGRSRLSCAASGFSFSSYG MHWVRQAPGKGLDWVALIWHDGTNKFYTD VKGRFTISRDNSKDTLFLQMNSLRVEDTAVYYCT KRAGWGDALDIWGQCTMTVSS	VH aa
SEQ ID NO: 214	DIQMTQSPSSLSASVGDRTITCQASQDISNYLN WYQQKPGKAPKLLIYDASNLETGVPSRFSGSGS ATDFTLTISLQSEDIATYYCQQQRIFGGGTKVEI K	VL aa
SEQ ID NO: 215	ggattcagcttcagtagttatggc	CDRH1 nuc
SEQ ID NO: 216	atatggcatgatggaactaataaa	CDRH2 nuc
SEQ ID NO: 217	acgaagcgggctggctggggtgatgctcttgataac	CDRH3 nuc
SEQ ID NO: 218	caggacattagcaactat	CDRL1 nuc
SEQ ID NO: 219	gatgcattc	CDRL2 nuc
SEQ ID NO: 220	ctgatctacgatgcattcaattggaa	CDRL2 long nuc
SEQ ID NO: 221	caacaacaaaggatt	CDRL3 nuc

SEQ ID NO: 222	cagggtgcagttggtggagctctgggggaggcgtggtccagcctggga ggtccctgagactctcctgtgcagcctctggattcagcttcagtagtt atggcatgcactgggtccgccaggctccaggcaaggggctggatt gggtggctcttatatggcatgatggaactaataaattttacacagact ccgtgaagggccgattcaccatctccagagacaattccaaggaca cactgttctgcaaataaacagctgagagttgaggacacggctgtgt attactgtacgaagcgggctggctggggtgatgctcttgatatctggg gccaaaggacaatggtcaccgtctcttcag	VH nuc
SEQ ID NO: 223	gacatccagatgaccagctccatcctcctgtctgcatctgtagg agacagagtcaccatcacttgccaggcgagtcaggacattagcaa ctatttaattggtatcagcagaaaccagggaagcccctaaactc ctgatctacgatgcatccaatttggaacaggggtcccatcaagggt cagtggaagtggatctgcgacagattttactctcaccatcagcagc ctgcagtctgaagacattgcaacatattactgtcaacaacaaaggga tttcggcgaggaggaccaaggtggagatcaaac	VL nuc
MGU8		
SEQ ID NO: 224	GFTFSNYG	CDRH1 aa
SEQ ID NO: 225	IWHDGTNK	CDRH2 aa
SEQ ID NO: 226	TKRGGWGDGSDI	CDRH3 aa
SEQ ID NO: 227	QDVDNY	CDRL1 aa
SEQ ID NO: 228	DAS	CDRL2 aa
SEQ ID NO: 229	LIYDASNLA	CDRL2 long aa
SEQ ID NO: 230	QQQRI	CDRL3 aa
SEQ ID NO: 231	QVQLVESGGGVVQPGRSLRLSCAAGGFTFSNY GMHWVRQAPGKGLEWVALIWHDGTNKFYAD SVKGRFTISRDNKNTLSLQMDSLTTEDTAIYFCT KRGGWGDGSDIWGQGTMVTVSS	VH aa
SEQ ID NO: 232	DIQMTQSPSSLSASVGDRTITCQASQDVDNYL NWKYQHKPGKAPKLLIYDASNLAATGVPSRFGSG SSTDFTLTISLSQSDDFATYYCQQQRIFGGGTRV EIK	VL aa
SEQ ID NO: 233	ggatttaccttcagtaactatggc	CDRH1 nuc
SEQ ID NO: 234	atatggcatgatggaactaataaa	CDRH2 nuc
SEQ ID NO: 235	acgaagcgaggtggctggggtgatggtctgataatc	CDRH3 nuc
SEQ ID NO: 236	caggacgttgacaactat	CDRL1 nuc
SEQ ID NO: 237	gatgcatcc	CDRL2 nuc
SEQ ID NO: 238	ctgatctacgatgcatccaatttggcg	CDRL2 long nuc
SEQ ID NO: 239	caacaacaaaggatt	CDRL3 nuc

SEQ ID NO: 240	caggtgcagctggaggagctggggaggcgtggccagcctggg aggccctaagactctcctgtgcagccggaggattacctcagtaac tatggcatgcactgggtccgccaggctccaggcaaggggctggag tgggtggcacttatatggcatgatggaactaataaattctatgcagac tccgtgaagggccgaltcaccatctccagagacaattccaagaac acgctgtctctgcaaatggacagcctgacaactgaggacacggct atatattctgtacgaagcgagggtggctgggggatgggtctgatattc ggggccaagggaacaatgggtcaccgtctctcag	VH nuc
SEQ ID NO: 241	gacatccagatgacccagctccatcctcctgtctgcattcttagg agacagagtcaccatcacttgccaggcgagtcaggacgttgacaa ctatttaattggatcagcataaaccagggaagcccctaagctcc tgatctacgatgcattcaatttggcgacaggggtcccatcaagggtc agtggagtgatcttcgacagatttactctcaccatcagcagcctg cagctgatgacttgcacatattactgtcaacaacaaggatttcc ggcggagggaaccagggtggaaatcaaac	VL nuc
MGU10		
SEQ ID NO: 242	GFAFSNYG	CDRH1 aa
SEQ ID NO: 243	IWHDGSLK	CDRH2 aa
SEQ ID NO: 244	TVWYLETPDDGFDI	CDRH3 aa
SEQ ID NO: 245	HGHTSKA	CDRL1 aa
SEQ ID NO: 246	VNSDGS	CDRL2 aa
SEQ ID NO: 247	QAWDSGIWV	CDRL3 aa
SEQ ID NO: 248	QVQLVESGGGVVQPGRLRLSCAASGFAFSNY GMNWVRQAPGKGLEWVAVIWHHDGSLKYYTQ SVKGRFTISRDNKNTLFLQMDSLSADDTAMYY CTVWYLETPDDGFDIWGRGTMVTSS	VH aa
SEQ ID NO: 249	QLVLTQPPSASASLGVSVTLTCTLSHGHTSKAIA WHQQQPGKGPRLMKVNSDGSHTKGAAPD RFGSTSGAERHFTISNLQSDDEADYYCQAWDS GIWVFGGGTKLTVL	VL aa
SEQ ID NO: 250	ggattcgcttcagcaattatggc	CDRH1 nuc
SEQ ID NO: 251	atttggcatgacggcagctctaaa	CDRH2 nuc
SEQ ID NO: 252	accgttgggtaccttgaaactcctgatgatgggttcgatatt	CDRH3 nuc
SEQ ID NO: 253	catggccacacctccaaagcc	CDRL1 nuc
SEQ ID NO: 254	gttaatagtgatggcagccac	CDRL2 nuc
SEQ ID NO: 255	caggcctgggacagtggcatttgggtt	CDRL3 nuc

SEQ ID NO: 256	caggtgcagctggaggagctgggggaggcgtggccagcctggg aggtccctgagactctcatgtgcagcctccggattcgcttcagcaat tatggcatgaactgggtccgccaggctccaggcaagggaactggaa tgggtggcagttatttggcatgacggcagtcctaaatattatacacagt ccgtgaagggccgattcacatctccagagacaatgccaagaac acgtgtttctcaaattggacagcctgagcgctgacgacacggctat gtattattgtaccgttgggtacctgaaactcctgatgatggttcgatatt tggggccgagggaacaatggtcaccgtctcgtcag	VH nuc
SEQ ID NO: 257	cagctgtcctgactcaaccgcctctgcctctgcctccctgggagt ctcggtcaccctcacctgtactctgagtcagggccacacctcaaaa gccatcgctggcatcaacagcagccagggaaggccctcgttat ttgatgaaagttaatagtgatggcagccacactaagggggccgctg tcctgatcgcttctcaggctctacttctggggctgagcgccacttca ccatctccaacctccagctgacgatgaggctgattattattgtcagg cctgggacagtggcatttgggtttcggcggagggaaccaagttgac cgtcctag	VL nuc
MGU11		
SEQ ID NO: 258	GFSFSSYG	CDRH1 aa
SEQ ID NO: 259	IWYDGTNK	CDRH2 aa
SEQ ID NO: 260	ANDIAGWGYDGSNA	CDRH3 aa
SEQ ID NO: 261	QSLVYSDGNTY	CDRL1 aa
SEQ ID NO: 262	KVS	CDRL2 aa
SEQ ID NO: 263	LIYKVSNRD	CDRL2 long aa
SEQ ID NO: 264	MQGTVGFT	CDRL3 aa
SEQ ID NO: 265	QVQLVESGGGVVQPGRLRLSCVASGFSFSSYG MHWVRQAPGKGLEWVAVIWIYDGTNKKYYADS VKGRFTISRDNTKNTLYLQMNSLRADDTAMYYC ANDIAGWGYDGSNAWGQGLTVTVSS	VH aa
SEQ ID NO: 266	LSPVTPGQPASISCKSSQSLVYSDGNTYLNWFQ QRPGQSPRRLIYKVSNRDSGVPDRFSGSGSGTD FTLKISRVEAEDVGVYYCMQGTGFTFGPGTTV DIK	VL aa
SEQ ID NO: 267	ggattcagcttcagtagctatggc	CDRH1 nuc
SEQ ID NO: 268	atatggtatgatggaaccaataaa	CDRH2 nuc
SEQ ID NO: 269	gcgaatgatattcggggtggggctatgatggtagtaatgcc	CDRH3 nuc
SEQ ID NO: 270	caaagcctcgtatatagtgatggaaacacctac	CDRL1 nuc
SEQ ID NO: 271	aaggtttct	CDRL2 nuc
SEQ ID NO: 272	ctaattataaggtttctaaccgggac	CDRL2 long nuc
SEQ ID NO: 273	atgcaagggtacagtggggttcact	CDRL3 nuc

SEQ ID NO: 274	cagggtcagctggaggagctctgggggaggcgtagtcagcctggg agggtccctgagactctcctgcgtagcctctggattcagctcagtagc tatggcatgcactgggtccgaggtccaggcaaggggctggag tgggtggcagttatattggtatgatggaaccaataaatactatgcagat tccgtgaagggccgattcaccatctccagagacaataccaagaac acgtgtacctgcaaatgaacagcctgagagcggacgacacggct atgtattactgtgcgaatgatattgcgggggtggggctatgatgtagta atgcctggggccagggaaccctggtcaccgtctcctcag	VH nuc
SEQ ID NO: 275	ctctccctgccgtcaccctggacagccggcctccatctcctgca agtctagtcaaagcctcgtatatagtgatggaaacacctactgaatt ggtttcagcagaggccaggccaatctccaaggcgctaattataa ggtttctaaccgggactctgggtccagacagattcagcggcagt gggtcaggcactgattcacactgaaaatcagcaggggtggaggctg aggatgttgggggttattactgcatgcaaggtacagtgggggtcactt cgccctgggaccacagtggatatcaaac	VL nuc
MGU12		
SEQ ID NO: 276	GFSFSSYG	CDRH1 aa
SEQ ID NO: 277	IWHDGSYS	CDRH2 aa
SEQ ID NO: 278	VKVEDYVRGSSHGGAFHI	CDRH3 aa
SEQ ID NO: 279	QTINNW	CDRL1 aa
SEQ ID NO: 280	KAS	CDRL2 aa
SEQ ID NO: 281	LIYKASSLE	CDRL2 long aa
SEQ ID NO: 282	QQYSSYWT	CDRL3 aa
SEQ ID NO: 283	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYG MHWVRQAPGKGPEWVAVIWHDGSYSYYADS VRGRFTISRDNSKNTLYLQMNSLRPEDTGMYHC VKVEDYVRGSSHGGAFHIWGQGTMTVSS	VH aa
SEQ ID NO: 284	DIQMTQSPSTLSASVGDRTITCRASQTINNW AWYQWKPGKAPELLIYKASSLESGVPSRFSGSGS GTEFTLTISLQPDDEFATYYCQQYSSYWTFGQG TKVDIK	VL aa
SEQ ID NO: 285	ggattcagctcagtagttatggc	CDRH1 nuc
SEQ ID NO: 286	attggcatgatggaagttacagt	CDRH2 nuc
SEQ ID NO: 287	gtgaaagttgaggattacgttagggggagttcacatgggggtgcttt catatc	CDRH3 nuc
SEQ ID NO: 288	cagactattaataactgg	CDRL1 nuc
SEQ ID NO: 289	taaggcgtct	CDRL2 nuc
SEQ ID NO: 290	ctgatctataaggcgtctagtttagaa	CDRL2 long nuc
SEQ ID NO: 291	caacagtatagtagttattggacg	CDRL3 nuc

SEQ ID NO: 292	caggtaactggtggaatctgggggaggcgtggccagcctggg aggccctgagactctcctgtgcagcctccggattcagctcagtagt tatggcatgcactgggtccgccaggctccaggcaagggccgga gtgggtggcagtgatttggcatgatggaagttacagttactatgcaga ctccgtgaggggcccattcaccatctccagagacaattccaagaa cacgctgtatctgcaaatgaacagcctgagacctgaggacacggg gatgtatcactgtgtgaaagttgaggattacgttagggggagttcaca tgggggtgctttcatatctggggccaagggaatggtcacctctc ttcag	VH nuc
SEQ ID NO: 293	gacatccagatgaccagtcctctccaccctgtctgcatctgtagg ggacagagtcaccatcactgcccgggcccagtcagactattaataac tggttggcctggtatcagtggaaaccggggaaagcccctgagctcc tgatctataaggcgtctagtttagaaagtggggtcccatcaaggtca gcggcagtgatctgggacagaattcactctcaccatcagcagcct gcagcctgatgattttgcaacttactgccaacagtatagtagttatt ggacgttcggccaagggaaccaaggtggacatcaaac	VL nuc
MGV3		
SEQ ID NO: 294	GFTVSDSY	CDRH1 aa
SEQ ID NO: 295	IYSGSST	CDRH2 aa
SEQ ID NO: 296	ARGPNDYRNRKYYYYMDV	CDRH3 aa
SEQ ID NO: 297	QSVDSPY	CDRL1 aa
SEQ ID NO: 298	GAS	CDRL2 aa
SEQ ID NO: 299	LIFGASIRA	CDRL2 long aa
SEQ ID NO: 300	HQYGNAPYI	CDRL3 aa
SEQ ID NO: 301	EVQVVESGGDLVQPGGSLRLSCAVYGFTVSDSY MSWVRQAPGKGLEWVSIVISGSSTYYIDSVKGR FTISRDRSKNTLYLQMNLTIRVEDTALYYCARGPN DYRNRKYYYYMDVWGKGTAVTVSS	VH aa
SEQ ID NO: 302	EIVLTQSPDTLSLSAGERVTLSCRASQSVDSPYLA WYQQRPGQTPRLLIFGASIRATDIPDRFSGGGS GTDFTLTISRLEPEDSGVYCHQYGNAPYIFGQG TKLEIK	VL aa
SEQ ID NO: 303	ggattcacgctcagtgacagctac	CDRH1 nuc
SEQ ID NO: 304	atctatagtggtagtagtaca	CDRH2 nuc
SEQ ID NO: 305	gcgagaggccctaatactacagaaatcgcaaatattactactac atggacgtc	CDRH3 nuc
SEQ ID NO: 306	cagagtgttgacagtcacctac	CDRL1 nuc
SEQ ID NO: 307	ggcgcctct	CDRL2 nuc
SEQ ID NO: 308	ctcatttttggcgcctctattagggcc	CDRL2 long nuc

SEQ ID NO: 309	caccagtatggtaacgcaccctacatt	CDRL3 nuc
SEQ ID NO: 310	gaggtgcaggtggaggagtctgggggagacttggtccagccgggg gggtccctgagactctcctgtgcagtctatggattcaccgtcagtga agctacatgagctgggtccgcccaggctccgggaaggggctgga gtgggtctcagttatctatagtggtagtagtacatactacatagactcc gtgaaggccgattcaccatctccagagacaggtccaagaacac cttgatcttcaaatgaacaccctgagagttgaggacacggctctta ttactgcgcgagaggccctaatactacagaaatcgaaatattact actacatggacgtctggggcaaagggaccgcggtcaccgtctcct cag	VH nuc
SEQ ID NO: 311	gaaattgtgtgacacagctctccagacaccctgtcctgtctgcagg ggaaagagtcaccctctcttgaggccagtcagagtggtgacagt ccctacttagcctggtatcagcaaagacctggccagactcccagg ctcctcattttgggtgcctctattaggccactgacatccagacagg ttcagtggtgggtgggtctgggacagacttactctcaccatcagca gactggaacctgaagattctggagtgtattactgtcaccagtatggta acgcaccctacattttggccaggggaccaagctggagatcaaac	VL nuc
SEQ ID NO: 312	KNNQNGQGHNMPNDPNRNVDENANANSA VKNNNNEEPPDKHIKEYLNKIQNSLSTEWSPCSV TCGNGIQVRIKPGSANKPKDEL DYANDIEKKICK MEKCS	CSP C-terminal peptide 282 – 383
SEQ ID NO: 313	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK	IgG1 CH1-CH2-CH3 aa
SEQ ID NO: 314	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC	IgG CK aa
SEQ ID NO: 315	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYP GAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTV PTECS	IgG CL aa

SEQ ID NO: 316	gcgtcgaccaagggcccatcggtcttccccctggcaccctcctcc aagagcacctctgggggacacagcgccctgggctgcctgggtcaa ggactacttccccgaacctgtgacgggtctctggaactcaggcgcc ctgaccagcggcgtgcacaccttcccggtgtcctacagtcctcag gactctactccctcagcagcgtggtgaccgtgccctccagcagctt gggcacccagacctacatctgaacgtgaatcacaagcccagca acaccaaggtggacaagagagttgagcccaatcttgtgacaaaa ctcacatgcccaccgtgccagcacctgaactcctgggggga ccgtcagtcttcttcccccaaaaccaaggacacctcatga tctccggaccctgaggtcacatgctggtggtggacgtgagcca cgaAgaCcctgaggtcaagttcaactggtacgtggacggcgtgga ggtgcataatgccaagacaaagccgcgggaggagcagtacaaca gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactg gtgaatggcaaggagtacaagtgaaggtctccaacaaagccct cccagcccccatcgagaaaaccatctccaagccaaagggcag ccccgagaaccacaggtgtacacctgcccccatcccgggagga gatgaccaagaaccaggtcagcctgacctgcctggtcaaaggctt ctatcccagcgacatcgccgtggagtgggagagcaatgggcagc cggagaacaactacaagaccacgcctcccgtgctggactccgac ggctccttcttctatagcaagctcaccgtggacaagagcaggtg gcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgc acaaccactacacgcagaagagccttccctgtccccgggtaaa	IgG1 CH1-CH2-CH3 nuc
SEQ ID NO: 317	cgTacGgtggctgcacatctgtcttcatcttcccgccatctgatga gcagttgaaatctggaactgcctctgtgtgtgctgctgaataacttc tatcccagagaggccaaagtacagtggaaaggtggataacgccttc caatcgggtaactcccaggagagtgctacagagcaggacagcaa ggacagcacctacagcctcagcagcacctgacgtgagcaaag cagactacgagaaacacaaagtctacgcctgcgaagtcacccat cagggcctgagctcgccgtcacaagagcttcaacaggggaga gtgt	IgG CK nuc
SEQ ID NO: 318	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcct ctgaggagctcaagccaacaaggccacactgggtgtgtctcataag tgacttctacccgggagccgtgacagtggcttgaaagcagatagc agccccgtcaaggcgggagtgagaccaccacacctccaac aaagcaacaacaagtacgcggccagcagctatctgagcctgacg cctgagcagtggaaagtcacagaagctacagctgccaggtcac gcatgaaggagcaccgtggagaagacagtggcccctacagaat gttca	IgG CL nuc
SEQ ID NO: 319	MENITSGFLGPLLVLQAGFFLLTRILTIPQSLDSW WTSLNFLGGTTVCLGQNSQSPTSNSHSPTSCPPT CPGYRWMCLRRFIIFLILLCLIFLLVLLDYQGML PVCPLIPGSSTTSTGPCRTCMTTAQGTSMYPSCC CTKPSDGNCTCIPISSWAFGKFLWEWASARFS WLSLLVPFVQWFVGLSPTVWLSVIWMMWYWG PSLYSILSPFLPLLIFFCLWVYI	HBsAg S domain

SEQ ID NO: 320	MMRKLAILSVSSFLFVEALFQEYQCYGSSSNTRVL NELNYDNAGTNLYNELEMNYYGKQENWYSLKK NSRSLGENDDGNNEDNEKLRKPKHKKLKQPAD GNPDP	N-terminus of CSP
SEQ ID NO: 321	KKLKQPA	N-terminal region of CSP
SEQ ID NO: 322	HKKLKQPAD	N-terminal region of CSP
SEQ ID NO: 323	KHKLKQPADG	N-terminal region of CSP
SEQ ID NO: 324	KHKLKQP	N-terminal region of CSP
SEQ ID NO: 325	RKPKHKKLKQP	N-terminal region of CSP
SEQ ID NO: 326	PKHKKLKQPADGN	N-terminal region of CSP
SEQ ID NO: 327	KPKHKKLKQPADGNP	N-terminal region of CSP
SEQ ID NO: 328	RKPKHKKLKQPADGNPD	N-terminal region of CSP
SEQ ID NO: 329	NEKLRKPKHKKLKQP	N-terminal region of CSP
SEQ ID NO: 330	NEKLRKPKHKKLKQPADG	N-terminal region of CSP
SEQ ID NO: 331	MLSKDIIKLLNEQVNKEMSSNLYMSMSSWCYT HSLDGAGLFLFDHAAEYEHAKKLIVFLNENNVP VQLTSISAPEHKFEGLTQIFQKAYEHEQHISESINN IVDHAIKGKDHATFNFLQWYVAEQHEEEVLFKD ILDKIELIGNENHGLYLADQYVKGIAKSRS	ferritin polypeptide
SEQ ID NO: 332	MEFLKRSFAPLTEKQWQEIDNRAREIFKTQLYGR KFVDVEGPYGWYAAHPLGEVEVLSDENEVVK WGLRKSLPLIELRATFTLDLWELDNLERGKPNVD LSSLEETVRKVAEFEDEVIFRGCEKSGVKGLLSFEER KIECGSTPKDLLEAIVRALSIFSKDGIEGPYTLVINT DRWINFLKEEAGHYPLEKRVEECLRGGKIITTPRIE DALVVSERGGDFKLILGQDLSIGYEDREKDAVRL FITETFTFQVVNPEALILLKF	encapsulin polypeptide:

In the VH/VL sequences the three sequences in bold show the CDR1, CDR2 and CDR3 in this order.

Claims

1. Antibody, or antigen-binding fragment thereof, binding to *P. falciparum* sporozoites, wherein the antibody, or the antigen binding fragment thereof, comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 64 – 68 and 70; (ii) according to SEQ ID NOs: 64 – 67 and 69 – 70; (iii) according to SEQ ID NOs: 82 – 86 and 88; (iv) according to SEQ ID NOs: 82 – 85 and 87 – 88; (v) according to SEQ ID NOs: 136 – 140 and 142; (vi) according to SEQ ID NOs: 136 – 139 and 141 – 142; (vii) according to SEQ ID NOs: 206 – 210 and 212; (viii) according to SEQ ID NOs: 206 – 209 and 211 – 212; (ix) according to SEQ ID NOs: 224 – 228 and 230; (x) according to SEQ ID NOs: 224 – 227 and 229 – 230; (xi) according to SEQ ID NOs: 258 – 262 and 264; (xii) according to SEQ ID NOs: 258 – 261 and 263 – 264; (xiii) according to SEQ ID NOs: 276 – 280 and 282; (xiv) according to SEQ ID NOs: 276 – 279 and 281 – 282; or (xv) according to SEQ ID NOs: 242 – 247.

2. The antibody, or the antigen binding fragment thereof, according to claim 1, wherein the antibody, or the antigen binding fragment thereof, comprises a heavy chain variable region (VH) and, optionally, a light chain variable region (VL), wherein the heavy chain variable region (VH) comprises or consists of an amino acid sequence according to any of SEQ ID NOs: 71, 89, 143, 213, 231, 248, 265, and 283; or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

3. The antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 2, wherein the antibody, or the antigen binding fragment thereof, comprises (i) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 71 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 72 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (ii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID

NO: 89 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 90 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 143 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 144 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 213 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 214 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (v) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 231 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 232 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 265 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 266 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%,

at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 283 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 284 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; or (viii) a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 248 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity and/or a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 249 or a functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

4. The antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 3, wherein the antibody, or the antigen binding fragment thereof, is a purified antibody, a single chain antibody, Fab, Fab', F(ab')₂, Fv or scFv.
5. The antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 4 for use as a medicament.
6. Use of the antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 4 in the manufacture of a medicament for the prevention and/or treatment of malaria.
7. A nucleic acid molecule comprising a polynucleotide encoding the antibody, or the antigen binding fragment thereof, according to any one of claims 1 – 4.
8. The nucleic acid molecule according to claim 7, wherein the polynucleotide sequence comprises or consists of a nucleic acid sequence according to any one of SEQ ID NOs: 73 – 81, 91 – 99, 145 – 153, 215 – 223, 233 – 241, 250 – 257, 267 – 275, 285 – 293; or a

functional sequence variant thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 88%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity.

9. A vector comprising the nucleic acid molecule according to claim 7 or claim 8.
10. A cell expressing the antibody, or the antigen binding fragment thereof, according to any of claims 1 - 7; or comprising the vector according to claim 12.
11. A pharmaceutical composition comprising the antibody, or the antigen binding fragment thereof, according to any of claims 1 - 4, the nucleic acid according to claim 7 or claim 8, the vector according to claim 9 and/or the cell according to claim 10; optionally further comprising a pharmaceutically acceptable excipient, diluent or carrier.
12. The nucleic acid according to claim 7 or claim 8, the vector according to claim 9, the cell according to claim 10, or the pharmaceutical composition according to claim 11 for use as a medicament.
13. Use of the nucleic acid according to claim 7 or claim 8, the vector according to claim 9, the cell according to claim 10, or the pharmaceutical composition according to claim 11 in the manufacture of a medicament for the prevention or treatment of malaria.
14. Use of the antibody, or the antigen binding fragment thereof, according to any of claims 1 - 4, the cell according to claim 10, or the pharmaceutical composition according to claim 11 for monitoring the quality of an anti-malaria vaccine by checking that the antigen of said vaccine contains the specific epitope in the correct conformation.
15. Use of the antibody, or the antigen binding fragment thereof, according to any of claims 1 - 4, the cell according to claim 10, or the pharmaceutical composition according to claim 11 in *in vitro* diagnosis of malaria.
16. A kit of parts comprising at least one antibody, or the antigen binding fragment thereof, according to any of claims 1 - 4, at least one nucleic acid according to any of claims 7 - 8, at

least one vector according to claim 9, at least one cell according to claim 10, or at least one pharmaceutical composition according to claim 11.