

5 Vaccine

10 The present invention relates to a simian derived adenoviral vector particularly encoding a new malaria antigen derived from the circumsporozoite protein of *Plasmodium falciparum*. The invention further relates to processes of preparing said viral vector and use of same in the treatment/prevention of malaria infection.

Malaria, is one of the world's major health problems with more than 2 to 4 million people dying from the disease each year.

15 One of the most acute forms of the disease is caused by the protozoan parasite, *Plasmodium falciparum* (*P. falciparum*) which is responsible for most of the mortality attributable to malaria.

20 The life cycle of *P. falciparum* is complex, requiring two hosts, man and mosquito for completion. The infection of man is initiated by the inoculation of sporozoites in the bloodstream through the bite of an infected mosquito. The sporozoites migrate to the liver and there infect hepatocytes where they differentiate, via the exoerythrocytic intracellular stage, into the merozoite stage which infects red blood cells (RBC) to initiate cyclical replication in the asexual blood stage. The cycle is completed by the
25 differentiation of a number of merozoites in the RBC into sexual stage gametocytes, which are ingested by the mosquito, where they develop through a series of stages in the midgut to produce sporozoites which migrate to the salivary gland.

30 The sporozoite stage of *Plasmodium* has been identified as a potential target of a malaria vaccine. Vaccination with deactivated (irradiated) sporozoite has been shown to induce protection against experimental human malaria (Am. J. Trop. Med. Hyg 24: 297-402, 1975). However, it is has not been possible practically and logistically to manufacture a vaccine for malaria for the general population based on this methodology, employing irradiated sporozoites.

35 The major surface protein of the sporozoite is known as circumsporozoite protein (CS protein). It is thought to be involved in the motility and invasion of the sporozoite during its passage from the initial site of inoculation by the mosquito into the circulation, where it migrates to the liver.

40 The CS protein of *Plasmodia* species is characterized by a central repetitive domain (repeat region) flanked by non-repetitive amino (N-terminus) and carboxy (C-terminus) fragments.

45 To date the most advanced malaria vaccine in the clinic is based on a lipoprotein particle (also known as a virus like particle) referred to as RTS,S. This particle contains a portion of the CS protein of *P. falciparum* substantially as corresponding to amino acids 207-395 of the CS protein of *P. falciparum* (strain NF54[3D7]) fused to the N-terminal of the S antigen from Hepatitis B. The S antigen may comprise a
50 portion of the preS2.

The RTS,S particle is usually delivered along with a strong adjuvant.

- 5 Nevertheless malaria vaccines have been proposed employing recombinant adenoviral vectors, for example WO 2004/055187 describes certain viral vectors including specific adeno 5 (Ad5) and adeno 35 (Ad 35) vectors, both derived from human adeno viruses, encoding CS protein.
- 10 There are more than 40 different serotypes of human adeno viruses, which vary in their pathogenicity, for example Ad5 is associated with mild respiratory infections in children, Ad4 and Ad7 are thought to be associated with respiratory infections in adults, and Ad40 is thought to cause diarrhoea in infants.
- 15 Immunity to adenovirus infections is thought to be life-long following infection. It is thought that pre-existing immunity to particularly Ad5 and Ad35 may result in the neutralisation of therapeutic adenoviral vectors based on human adeno viruses. This may reduce the therapeutic effectiveness of the vector as the vector is prevented from entering cells and manufacturing the relevant antigen *in vivo*.
- 20 The present invention is thought to reduce the issues of pre-existing immunity by providing a vaccine for prevention and/or treatment of malaria comprising: a replication deficient simian adenoviral vector C7 (also referred to as Pan 7 or CV-33) encoding a protein comprising CS protein from *P. falciparum* or a fragment thereof, for example as shown in Seq ID No: 1 or Seq ID No: 3.
- 25

Brief description of the Sequences

- | | | | |
|------------|------------|--|---|
| Seq ID No: | 1 | An amino acid sequence of a protein/antigen derived from CS protein of <i>P. falciparum</i> (referred to herein as Ade2 protein) | |
| 30 | Seq ID No: | 2 | A nucleic acid sequence encoding the protein of Seq ID No: 1 (referred herein as Ade2 gene) |
| | Seq ID No: | 3 | An alternative amino acid sequence of a protein/antigen derived from CS protein of <i>P. falciparum</i> (referred herein as Ade1 protein) |
| 35 | Seq ID No: | 4 | A nucleic acid sequence encoding the protein of Seq ID No: 3 (referred herein as Ade1 gene) |
| | Seq ID No: | 5 | Capsid protein sequence from Chimp Adeno 7(seq ID No 17 from WO 03/046124) |
| 40 | Seq ID No: | 6 | An amino acid sequence from Chimp Adeno 7(seq ID No 20 from WO 03/046124) |
| | Seq ID No: | 7 | An amino acid sequence from <i>P. falciparum</i> CS protein |
| | Seq ID No: | 8 | An amino acid sequence from <i>P. falciparum</i> CS protein |
| | Seq ID No: | 9 | An amino acid sequence from <i>P. falciparum</i> CS protein |
| 45 | Seq ID No: | 10 | An amino acid sequence from <i>P. falciparum</i> CS protein |
| | Seq ID No: | 11 | Nucleotide sequence for CpG 1826 |
| | Seq ID No: | 12 | Nucleotide sequence for CpG 1758 |
| | Seq ID No: | 13 | Nucleotide sequence for a CpG |
| | Seq ID No: | 14 | Nucleotide sequence for CpG 2006 |
| 50 | Seq ID No: | 15 | Nucleotide sequence for CpG 1668 |
| | Seq ID No: | 16 | Nucleotide sequence for CpG 5456 |
| | Seq ID No: | 17 | Shows the nucleotide sequence of an alternative expression cassette to Ade2 expression cassette and cloned into C7 adenoviral vector |

- 5 Seq ID No: 18 Shows the nucleotide sequence of the Ade2 expression cassette, cloned into C7 adenoviral vector
- Seq ID No: 19 Shows the complete nucleotide sequence of the synthetic recombinant vector C7 -Ade2.

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Brief description of the Figures.

- Figure 1 Shows a plasmid map for pCR2.1-Ade2
- 15 Figure 2 Shows the plasmid map for pShuttle6-Ade2
- Figure 3 Shows plasmid maps for pC7000-CMV Ade2
- 20 Figures 4 to 7 Show comparison between the CS-specific T cell responses induced by C7 Ade1 & C7 Ade2 in C57Bl/6 mice.
- Figures 8 to 11 Show comparison between the CS-specific T cell responses induced by C7 Ade2 and Ad5 Ade2 in C57Bl/6 mice.
- 25 Figures 12 to 15 Show comparison between the CS-specific T cell responses induced by C7 Ade1 and Ad5 Ade1 in C57Bl/6 mice.
- Figure 16 Shows anti-CS antibody responses determined by ELISA in C57Bl/6 mice.
- 30 Figures 17 and 18 Show kinetics of the CS-specific CD8 T cell responses induced by C7-Ade2 in CB6F1 mice.
- 35 Figures 19 and 20 Show kinetics of the CS-specific CD4 T cell responses induced by C7-Ade2 in CB6F1 mice.
- Figures 21 and 22 Show cytokine profile of the CS-specific CD8 T cell responses induced by C7-Ade2 in CB6F1 mice.
- 40 Figures 23 and 24 Show cytokine profile of the CS-specific CD4 T cell responses induced by C7-Ade2 in CB6F1 mice.
- Figures 25 and 26 Show kinetics of the CS-specific CD8 T cell responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.
- 45 Figures 27 and 28 Show kinetics of the CS-specific CD4 T cell responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.
- 50 Figure 29 Shows kinetics of the HBs-specific CD8 T cell responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.

5	Figure 30	Shows kinetics of the HBs-specific CD4 T cell responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.
10	Figures 31 and 32	Show cytokine profile of the CS-specific CD8 T cell responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.
15	Figure 33	Cytokine profile of the HBs-specific CD8 T cell responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.
20	Figures 34 and 35	Cytokine profile of the CS-specific CD4 T cell responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.
	Figure 36	Cytokine profile of the HBs-specific CD4 T cell responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.
25	Figures 37 and 38	Show antibody responses induced by C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice.
30	Figures 39 to 41	Show kinetics of the CS- & HBs-specific CD8 T cell responses induced by co-formulation C7-Ade2+ RTS,S/AS01B in CB6F1 mice.
35	Figures 42 to 44	Show kinetics of the CS- & HBs-specific CD4 T cell responses induced by co-formulation C7-Ade2+ RTS,S/AS01B in CB6F1 mice.
40	Figures 45 to 47	Show cytokine profile of the CS- & HBs-specific CD8 T cell responses induced by co-formulation C7-Ade2+ RTS,S/AS01B in CB6F1 mice.
	Figures 48 to 50	Show cytokine profile of the CS- & HBs-specific CD4 T cell responses induced by co-formulation C7-Ade2+ RTS,S/AS01B in CB6F1 mice.
45	Figures 51 and 52	Show antibody responses induced by co-formulation C7-Ade2+ RTS,S/AS01B in CB6F1 mice.
50	Figures 53 to 55	Show kinetics of the CS- & HBs-specific CD8 T cell responses induced by C7-Ade2, RTS,S and AS01B responses in CB6F1 mice.
	Figures 56 to 58	Show kinetics of the CS- & HBs-specific CD4 T cell responses induced by C7-Ade2, RTS,S and AS01B responses in CB6F1 mice.

- 5 Figures 59 to 61 Show cytokine profile of the CS- & HBs-specific CD8 T cell responses induced by C7-Ade2, RTS,S and AS01B responses in CB6F1 mice.
- 10 Figures 62 to 64 Show cytokine profile of the CS- & HBs-specific CD4 T cell responses induced by C7-Ade2, RTS,S and AS01B responses in CB6F1 mice.
- 15 Figures 65 and 66 Show antibody responses induced by C7-Ade2, RTS,S and AS01B responses in CB6F1 mice.
- 20 Figures 67 and 68 Show kinetics of the CS-specific CD8 T cell responses induced by synthetic C7 Ade2 in CB6F1 mice.
- 25 Figures 69 and 70 Show kinetics of the CS-specific CD4 T cell responses induced by synthetic C7 Ade2 in CB6F1 mice.
- 30 Figures 71 and 72 Show cytokine profile of the CS-specific CD8 T cell responses induced by synthetic C7 Ade2 in CB6F1 mice.
- 35 Figures 73 and 74 Show cytokine profile of the CS-specific CD4 T cell responses induced by synthetic C7 Ade2 in CB6F1 mice.

40 The sequence and preparation of C7 is described in WO 2003/046124. Sequence ID Nos: 6 (penton sequence), 9 (nucleic acid sequence), 10 & 11 (hexon sequence), & 12 (fibre protein) of WO 2003/046124 are incorporated by reference. The deposit number for C7 is [ATCC VR-593].

45 The characteristics and properties of any given adenoviral vector are often individual, although there is a hypothesis that vectors may be grouped into families and that adenoviral vectors within a given family may have similar characteristics.

50 Employing C7 is thought to be particularly advantageous as it seems to be more stable once the protein encoding gene is inserted than certain other known vectors, for example C6 also described in WO 2003/046124. That is to say C7 is thought to be less prone to re-organisation. Of course it is very important that any adenoviral vector employed in a vaccine is stable because pharmaceutical products need to be well characterised and shown to be stable and safe before they can be marketed.

55 Pre-existing immunity to C7 is thought to be very low and thus the risk of neutralisation of the viral vector after the first administration to a patient is low.

60 Furthermore, there are thought to be one or more other properties of C7 that are likely to make it particularly suitable for administration to humans and/or for generating a favourable immune response *in vivo*.

65 In one aspect the invention employs a synthetic C7 viral vector, which may be particularly suitable for gaining regulatory approval for administration to humans.

5 In one aspect the malaria antigen component from the CS protein has the last 12 to 14 amino acids removed.

In one aspect the malaria antigen encoded by the adenoviral vector is modified to remove potential glycosylation sites, for example the amino acid alanine may replace
10 a serine, such as shown in position about 379 of Seq ID No: 1.

In one aspect the invention the protein/antigen employed comprises the following amino acids;

15 NNGDNGREGKDEDKRDGNN [Seq ID No: 7]

optionally located at about amino acid 81 to 99.

In one aspect the protein/antigen encoded comprises the amino acids:

20 AIGL [Seq ID No: 8]

for example at the C terminus.

25 In one aspect the invention employs a protein comprising the following amino acids:
PNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNVDPN
ANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNAN
PNANPNANPNANPNANPNANPNANPN

[Seq ID No: 9]

30 In one aspect the invention employs a protein comprising the following amino acids:

35 NANP NVDP NANP NVDP NANP NVDP NANP NANP NANP NANP
NANP NANP NANP NANP NANP NANP NANP NVDP NANP NANP
NANP NANP NANP NANP NANP NANP NANP NANP NANP NANP
NANP NANP NANP NANP NANP NANP

[Seq ID No: 10]

40 In a further aspect the protein/antigen employed comprises the sequences of Seq ID No. 7 and/or Seq ID No. 8 and/or Seq ID No 9.

In a further aspect the protein/antigen employed comprises the sequences of Seq ID No. 7 and/or Seq ID No. 8 and/or Seq ID No 10.

45 In one aspect the protein/antigen encoded is Seq ID No: 1 or 3.

The protein sequence given in Seq ID No: 1 is new and forms an aspect of the invention.

50 Polynucleotide encoding the protein sequence of Seq ID No:1 also forms an aspect of the invention, in particular the polynucleotide sequence of Seq ID No: 2. This polynucleotide sequence (ID No: 2) is already codon-optimized for expression in, humans.

55

- 5 Optionally a polynucleotide sequence encoding the protein of Seq ID No: 1 may be codon-optimized.

10 The invention also extends to vectors/plasmids/hosts employed in the preparation of the novel hybrid fusion protein of Seq ID No: 1 or employed in the preparation of a viral vector according to the invention.

15 When preparation and isolation of the protein is required a suitable plasmid can be employed to insert the sequence encoding for the protein into a suitable host for synthesis. An example of a suitable plasmid is pRIT15546 a 2 micron-based vector for carrying a suitable expression cassette. The plasmid will generally contain an in-built marker to assist selection, for example a gene encoding for antibiotic resistance or LEU2 or HIS auxotrophy.

20 Host cells can be prokaryotic or eukaryotic but preferably, are yeast, for example *Saccharomyces* (for example *Saccharomyces cerevisiae* such as DC5 in ATCC data base (accession number 20820), under the name RIT DC5 cir(o). Depositor: Smith Kline-RIT) and non- *Saccharomyces* yeasts. These include *Schizosaccharomyces* (eg *Schizosaccharomyces pombe*) *Kluyveromyces* (eg *Kluyveromyces lactis*), *Pichia* (eg *Pichia pastoris*), *Hansenula* (eg *Hansenula polymorpha*), *Yarrowia* (eg *Yarrowia lipolytica*) and *Schwanniomyces* (eg *Schwanniomyces occidentalis*).

In one aspect the invention provides use of the vectors according to the invention or a protein of Seq ID No 1 for the treatment or prevention of malaria.

30 In one aspect the invention provides a pharmaceutical formulation comprising a viral vector according to the invention and an excipient such as an isotonic carrier suitable for injection. Suitable excipients are discussed in more detail below.

In one embodiment a formulation comprises:

- 35
- an adeno viral vector according to the invention,
 - a malaria antigen such as a lipoprotein particle particularly RTS,S, and
 - optionally an adjuvant for example comprising a saponin and/or 3D-MPL.

40 When the vector encodes the sequence of Seq ID No: 1 the vector is particularly suitable for use in a treatment regime with the protein known as RTS,S. This is because the protein encoded by the adenoviral vector corresponds as closely as possible to the "RT" component in RTS,S. Use of the vector in a regime with RTS,S is thought to have the ability to reinforce efficiently the efficacy of RTS,S.

45 The viral vectors described herein are suitable for use as component for a malaria vaccine. The viral vectors of the invention may need to be used in combination with other components including other antigens to provide adequate protection against infection. Nevertheless the vectors of the present invention are suitable for use at least as a component of vaccine or treatment regime.

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5 **RTS,S**

RTS,S can be prepared as described in WO 93/10152 (eg from *P. falciparum* NF54/3D7 strain). The nucleotide sequence for the RTS expression cassette and predicted translation product is provided in Figure 9 of WO 93/10152 (referred to therein as RTS*).

10

In the context of this specification excipient, refers to a component in a pharmaceutical formulation with no therapeutic effect in its own right. A diluent or carrier falls within the definition of an excipient. Suitable carriers include PBS, saline and the like. Adjuvants are also within this definition of excipient because whilst

15 adjuvants may have a physiological effect *in vivo* this effect is general and in the absence of a therapeutic component is not a specific therapeutic effect.

Adjuvants

20 Particular adjuvants are those selected from the group of metal salts, oil in water emulsions, Toll like receptors agonist, (in particular Toll like receptor 2 agonist, Toll like receptor 3 agonist, Toll like receptor 4 agonist, Toll like receptor 7 agonist, Toll like receptor 8 agonist and Toll like receptor 9 agonist), saponins or combinations thereof.

25

In an embodiment the adjuvant is a Toll like receptor (TLR) 4 ligand, for example an agonist such as a lipid A derivative particularly monophosphoryl lipid A or more particularly 3-deacylated monophosphoryl lipid A (3D – MPL).

30 3-Deacylated monophosphoryl lipid A is known from US patent No. 4,912,094 and UK patent application No. 2,220,211 (Ribi) and is available from Ribi Immunochem, Montana, USA.

3D-MPL is sold under the trademark MPL® by Corixa corporation and primarily promotes CD4+ T cell responses with an IFN- γ (Th1) phenotype. It can be produced according to the methods disclosed in GB 2 220 211 A. Chemically it is a mixture of 3-deacylated monophosphoryl lipid A with 3, 4, 5 or 6 acylated chains. Generally in the compositions of the present invention small particle 3D-MPL is used. Small particle 3D-MPL has a particle size such that it may be sterile-filtered through a

40 0.22 μ m filter. Such preparations are described in WO 94/21292. Synthetic derivatives of lipid A are known and thought to be TLR 4 agonists including, but not limited to:

45 **OM174** (2-deoxy-6-O-[2-deoxy-2-[(R)-3-dodecanoyloxytetradecanoylamino]-4-o-phosphono- β -D-glucopyranosyl]-2-[(R)-3-hydroxytetradecanoylamino]- α -D-glucopyranosyldihydrogenphosphate), (WO 95/14026)

OM 294 DP (3S, 9 R) –3-[(R)-dodecanoyloxytetradecanoylamino]-4-oxo-5-aza-9(R)-[(R)-3-hydroxytetradecanoylamino]decan-1,10-diol,1,10-bis(dihydrogenophosphate)

50 (WO99 /64301 and WO 00/0462),

5

OM 197 MP-Ac DP (3S-, 9R) -3-[(R) -dodecanoyloxytetradecanoylamino]-4-oxo-5-aza-9-[(R)-3-hydroxytetradecanoylamino]decan-1,10-diol,1 -dihydrogenophosphate 10-(6-aminohexanoate) (WO 01/46127).

- 10 Typically when 3D-MPL is used the antigen and 3D-MPL are delivered in an oil in water emulsion or multiple oil in water emulsions. The incorporation of 3D-MPL is advantageous since it is a stimulator of effector T-cells responses.

- 15 Other TLR4 ligands which may be used are alkyl Glucosaminide phosphates (AGPs) such as those disclosed in WO 9850399 or US 6303347 (processes for preparation of AGPs are also disclosed), or pharmaceutically acceptable salts of AGPs as disclosed in US 6764840. Some AGPs are TLR4 agonists, and some are TLR4 antagonists. Both are thought to be useful as adjuvants.

- 20 Another immunostimulant for use in the present invention is Quil A and its derivatives. Quil A is a saponin preparation isolated from the South American tree *Quilaja Saponaria Molina* and was first described as having adjuvant activity by Dalsgaard *et al.* in 1974 ("Saponin adjuvants", Archiv. für die gesamte Virusforschung, Vol. 44, Springer Verlag, Berlin, p243-254). Purified fragments of
25 Quil A have been isolated by HPLC which retain adjuvant activity without the toxicity associated with Quil A (EP 0 362 278), for example QS7 and QS21 (also known as QA7 and QA21). QS21 is a natural saponin derived from the bark of *Quillaja saponaria* Molina which induces CD8⁺ cytotoxic T cells (CTLs), Th1 cells and a predominant IgG2a antibody response.

- 30 Particular formulations of QS21 have been described which further comprise a sterol (WO 96/33739). The ratio of QS21: sterol will typically be in the order of 1:100 to 1 : 1 weight to weight. Generally an excess of sterol is present, the ratio of QS21 : sterol being at least 1 : 2 w/w. Typically for human administration QS21 and sterol will be
35 present in a vaccine in the range of about 1 µg to about 100 µg, such as about 10 µg to about 50 µg per dose.

- Liposomal formulations generally contain a neutral lipid, for example phosphatidylcholine, which is usually non-crystalline at room temperature, for
40 example egg yolk phosphatidylcholine, dioleoyl phosphatidylcholine or dilauryl phosphatidylcholine. The liposomes may also contain a charged lipid which increases the stability of the liposome-QS21 structure for liposomes composed of saturated lipids. In these cases the amount of charged lipid is often 1-20% w/w, such as 5-10%. The ratio of sterol to phospholipid is 1-50% (mol/mol), such as 20-25%.

- 45 These compositions may contain MPL (3-deacylated mono-phosphoryl lipid A, also known as 3D-MPL). 3D-MPL is known from GB 2 220 211 (Ribi) as a mixture of 3 types of de-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains and is manufactured by Ribi Immunochem, Montana.

50

5 The saponins may in the form of micelles, mixed micelles (generally, but not exclusively with bile salts) or may be in the form of ISCOM matrices (EP 0 109 942), liposomes or related colloidal structures such as worm-like or ring-like multimeric complexes or lipidic/layered structures and lamellae when formulated with cholesterol and lipid, or in the form of an oil in water emulsion (for example as in WO 95/17210).

10

Usually, the saponin is presented in the form of a liposomal formulation, ISCOM or an oil in water emulsion.

15

Immunostimulatory oligonucleotides may also be used. Examples oligonucleotides for use in adjuvants or vaccines of the present invention include CpG containing oligonucleotides, generally containing two or more dinucleotide CpG motifs separated by at least three, more preferably at least six or more nucleotides. A CpG motif is a Cytosine nucleotide followed by a Guanine nucleotide. The CpG oligonucleotides are typically deoxynucleotides. In one embodiment the internucleotide in the
20 oligonucleotide is phosphorodithioate, or more preferably a phosphorothioate bond, although phosphodiester and other internucleotide bonds are within the scope of the invention. Also included within the scope of the invention are oligonucleotides with mixed internucleotide linkages. Methods for producing phosphorothioate oligonucleotides or phosphorodithioate are described in US 5,666,153, US 5,278,302
25 and WO 95/26204.

Examples of oligonucleotides are as follows:

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TCC ATG ACG TTC CTG ACG TT (CpG 1826)	[Seq ID No: 11]
TCT CCC AGC GTG CGC CAT (CpG 1758)	[Seq ID No: 12]
ACC GAT GAC GTC GCC GGT GAC GGC ACC ACG	[Seq ID No: 13]
TCG TCG TTT TGT CGT TTT GTC GTT (CpG 2006)	[Seq ID No: 14]
TCC ATG ACG TTC CTG ATG CT (CpG 1668)	[Seq ID No: 15]
TCG ACG TTT TCG GCG CGC GCC G (CpG 5456),	[Seq ID No: 16]

the sequences may contain phosphorothioate modified internucleotide linkages.

35

Alternative CpG oligonucleotides may comprise one or more sequences above in that they have inconsequential deletions or additions thereto.

40

The CpG oligonucleotides may be synthesized by any method known in the art (for example see EP 468520). Conveniently, such oligonucleotides may be synthesized utilising an automated synthesizer.

Examples of a TLR 2 agonist include peptidoglycan or lipoprotein.

45

Imidazoquinolines, such as Imiquimod and Resiquimod are known TLR7 agonists. Single stranded RNA is also a known TLR agonist (TLR8 in humans and TLR7 in mice), whereas double stranded RNA and poly IC (polyinosinic-polycytidylic acid - a commercial synthetic mimetic of viral RNA) are exemplary of TLR 3 agonists. 3D-MPL is an example of a TLR4 agonist whilst CpG is an example of a TLR9 agonist.

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- 5 An immunostimulant may alternatively or in addition be included. In a one embodiment this immunostimulant will be 3-deacylated monophosphoryl lipid A (3D-MPL).

In one aspect the adjuvant comprises 3D-MPL.

10

In one aspect the adjuvant comprises QS21.

In one aspect the adjuvant comprises CpG.

- 15 In one aspect the adjuvant is formulated as an oil in water emulsion.

In one aspect the adjuvant is formulated as liposomes.

- 20 Adjuvants combinations include 3D-MPL and QS21 (EP 0 671 948 B1) oil in water emulsions or liposomal formulations comprising 3D-MPL and QS21 or 3D-MPL formulated with other carriers (EP 0 689 454 B1). Other preferred adjuvant systems comprise a combination of 3D-MPL, QS21 and a CpG oligonucleotide as described in US 6558670 and US 6544518.

25 **Formulations**

Vaccine preparation is generally described in New Trends and Developments in Vaccines, edited by Voller et al., University Park Press, Baltimore, Maryland, U.S.A., 1978. Encapsulation within liposomes is described, for example, by Fullerton, U.S. Patent 4,235,877.

30

The formulations of the present invention may be used for both prophylactic and therapeutic purposes. Accordingly the invention provides a vaccine composition as described herein for use in medicine, for example, for the treatment and/or prophylaxis of malaria.

35

In one aspect the invention provides a composition comprising a C7 adenoviral vector according to the invention and a malaria antigen such as RTS,S or the novel antigen of Seq ID No: 1 or virus like particles of the same and an excipient, optionally in the presence of an adjuvant.

40

Immunogenic in the context of this specification is intended to refer to the ability to elicit an immune response, wherein said response is specific to a malaria component in the relevant formulation. This response may require the presence of a suitable adjuvant and/or boosting. A booster, for example, comprising a dose similar or less than the original dose, may be required to obtain an appropriate immunogenic response.

45

The composition/pharmaceutical formulations according to the invention may also include in admixture one or more further antigens such as those derived from *P.*

- 50 *falciparum* and/or *P. vivax*, for example wherein the antigen is selected from DBP,

- 5 PvTRAP, PvMSP2, PvMSP4, PvMSP5, PvMSP6, PvMSP7, PvMSP8, PvMSP9, PvAMA1 and RBP or fragment thereof.

Other example, antigens derived from *P. falciparum* include, PfEMP-1, Pfs 16 antigen, MSP-1, MSP-3, LSA-1, LSA-3, AMA-1 and TRAP. Other *Plasmodium* antigens
 10 include *P. falciparum* EBA, GLURP, RAP1, RAP2, Sequestrin, Pf332, STARP, SALSA, PfEXP1, Pfs25, Pfs28, PFS27/25, Pfs48/45, Pfs230 and their analogues in other *Plasmodium* spp.

15 The invention also relates to use of C7 for encoding a malaria antigen, for example particularly as described herein for the treatment and/or prevention of malaria, or for the manufacture of a medicament for same.

The invention also includes a method of treatment comprising administering a therapeutically effective amount of one or more aspects of the invention.
 20 Optionally the C7 viral vector according to the invention may be co-administered or co-formulated with a malaria antigen such as RTS,S or the antigen of Seq ID No. 1, optionally in the presence of an adjuvant for example comprising 3D-MPL and/or a saponin such as QS21.

25 The C7 vector may also be co-administered or co-formulated with another adenoviral vector of a different serotype and/or origin, encoding the same of different antigens.

The invention also extends to use of any aspect defined herein in a prime boost regime, for example wherein the priming dose or doses is/are given at a timepoint zero
 30 (and subsequent primes within for example 3 months) and a boost is given, for example at about 4, 5, 6, 7, 8, 9, 10, 11 or 12 weeks after the last priming dose, optionally with a further boosting shot or shots given up to one year after said first boosting shot.

35 Advantageously one or more aspects of the invention, including the combination vaccine described above, stimulate specific humoral (that is antibody responses) and/or cellular immune responses (such as CD8+ and/or CD4+) such as antibody responses and CD 8+ and/or CD4+ responses, particularly CD8+ and antibody responses. That is to say responses specific to the CS protein and/or S antigen (as
 40 appropriate).

This type of balanced immune response may be required to give so called sterile protection against malarial infection.

45 Furthermore antibody responses for combinations may be augmented in relation to antibody responses to adjuvanted protein only regime schemes.

In one embodiment the invention provides use of C7 as the prime or boost in a prime boost regime with:

- 50
- a C7 adenoviral vector encoding the same or different malaria antigen,
 - another viral vector such as a human adenoviral vector such as Ad5 or Ad35 encoding a malaria antigen such as a CS protein from *P. falciparum* or simian adenoviral vector of a different serotype (ie not C7), and/or

- 5 • a malaria antigen such as RTS,S and an adjuvant, for example comprising a saponin and/or 3D-MPL, as the complementary component of the regime.

10 The invention also provides any of the aspects herein described for the manufacture of a medicament for the treatment and/or prevention of malarial infection.

Quantities

15 The amount of 3D-MPL used is generally small, but depending on the vaccine formulation may be in the region of 1-1000µg per dose, for example 1-500µg per dose, and such as in the range 1 to 100µg per dose, such as 50 or 25µg per dose.

20 The amount of CpG or immunostimulatory oligonucleotides in the adjuvants or vaccines of the present invention is generally small, but depending on the vaccine formulation may be in the region of 1-1000µg per dose, for example 1-500µg per dose, and such as in the range 1 to 100µg per dose.

25 The amount of saponin for use in the adjuvants of the present invention may be in the region of 1-1000µg per dose, for example 1-500µg per dose, such as 1-250µg per dose, and particularly in the range 1 to 100µg per dose such as 50 or 25µg per dose.

When protein is administered the dose may, for example be 1 to 500 µg such as 10 to 100 µg, particularly 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75 or 80 µg per dose.

30 When adenoviral vectors are administered the dose may, for example be 10^3 to 10^{16} vpu such as 10^6 to 10^{10} vpu.

When a combination is employed then the amounts employed for each component of the combination may correspond to the dose given for that component alone.

35 The invention also extends to kits comprising the elements employed in combinations according to the invention.

40 The invention further relates to a process for preparing an adenoviral vector according to the invention and formulations comprising the same.

The invention also relates to a method of producing the protein of Seq ID No 1.

In the context of this specification comprising is to be interpreted as including.

45 The invention extends to embodiments which correspond to embodiments described herein as comprising certain element but consisting or consisting essentially of the relevant elements.

50 Discussion in the background section of this specification is provided for the purpose of putting the invention in context. It is not to be taken as admission about what is known in the art and in particular is not an admission of what constitutes common general knowledge.

5

The examples below are shown to illustrate the methodology, which may be employed in the invention.

EXAMPLES

10

Example 1

The synthetic gene was prepared by a company Medigenomix. The gene was cloned into pCR2.1-TOPO-TA cloning vector (Invitrogen see Figure 1). This vector was digested with *NotI* and *BamHI* and a recombinant shuttle plasmid vector (-Ade2) was created. The map of the shuttle plasmid is shown in Figure 2.

Description of the expression cassette and methodology for virus rescue

The expression cassette contains the cytomegalovirus (CMV) early promoter and first exon, an intron derived from the plasmid pCI (purchased from Promega) the DNA encoding Ade2, and the rabbit globin polyadenylation signal. The complete cassette is flanked by recognition sites for the restriction enzymes I-CeuI and PI-SceI respectively. The expression cassettes were excised from the shuttle plasmid using I-CeuI and PI-SceI and introduced into a plasmid molecular clone of an E1 deleted genome of SAdV-24 (ie C7) – pC7 000 pkGFP as described (Roy et al. Hum Gene Ther. (2004) 5:519-530) to obtain the plasmid shown in Figure 3

The plasmid molecular clone DNA was linearized by digesting with the restriction enzyme PacI and transfected into HEK 293 cells to rescue recombinant adenovirus. The adenoviruses were propagated, amplified and purified using standard techniques.

The sequences of the expression cassette for (Ade2) from the I-CeuI to the PI-SceI recognition sites is shown in Seq ID Nos: 18.

Example 2

Immunogenicity of the C7-Ade1 & C7-Ade2 in C57Bl/6 mice

C57Bl/6 mice were immunized once intramuscularly with a dose range (10e10, 10e9, 10e8 viral particles) of the C7 chimpadenoviruses expressing either of the construct Ade1 or Ade2. As positive controls, some mice were immunized with the human adenovirus 5 (at the dose of 10e9 and 10e8) expressing either of the construct Ade1 or Ade2. As negative controls, some mice were immunized with empty C7 & empty Ad5 viral vectors.

Peripheral blood was collected and pooled on days 14, 28, 34 and 49 post-immunization and the Ag-specific CD4 & CD8 T cell responses producing IL-2 and/or IFN-gamma were measured by flow cytometry, after overnight in vitro restimulation with pools of 15mer peptides covering the sequences of interest, i.e. the N-terminal region (N-term) or C-terminal region (C-term) of the CS protein. As negative controls, some cells were also cultured overnight in vitro in culture medium (unstimulated). The Ag-specific responses were calculated by subtracting the average

- 5 cytokine response produced by unstimulated cells from the average cytokine response produced by the peptide-stimulated cells.

The results indicate that under the experimental conditions described above, both constructs induced CS-specific CD4 and CD8 T cell responses (Figures 4 to 15). Of
 10 note, C-term specific CD8 T cell responses were only detected in mice immunized with adenoviruses carrying the Ade2 insert (Figure 4 & 8). In particular, these C-term specific CD8 T cell responses were similar in mice immunized with either 10e10vp of C7 Ade2 or 10e9vp of Ad5 Ade2 (Figure 8).

- 15 In addition, the anti-CS antibody responses were determined by ELISA on sera collected 48 days post-immunization. In particular, it is the total Ig response against the R32LR polypeptide (i.e. which covers the middle portion of *P. falciparum* CSP) that was measured (Mettens et al., Vaccine 2008). The results indicate that a single
 20 immunization with C7 Ade1 or C7 Ade2 induces low levels of R32LR-specific antibody response. The intensity of this response correlates with the number of viral particles used for immunization (dose range effect).

Example 3

Immunogenicity of the C7-Ade2 in CB6F1 mice

- 25 CB6F1 mice were immunized once intramuscularly with a dose range (10e10, 10e9, 10e8 viral particles) of the C7 chimpadenovirus expressing the Ade2 construct (5 pools of mice/group). Peripheral blood was collected and pooled on days 21, 28 and 35 post-immunization and the CS C-term and CS N-term specific CD4 & CD8 T cell
 30 responses producing IL-2 and/or IFN-gamma were measured by flow cytometry, after overnight in vitro restimulation with pools of 15mer peptides covering the sequences of interest, i.e. the N-terminal region (N-term) or C-terminal region (C-term) of the CS protein. As negative controls, some cells were also cultured overnight in vitro in culture medium (unstimulated). The Ag-specific responses were calculated by
 35 subtracting the average cytokine response produced by unstimulated cells from the average cytokine response produced by the peptide-stimulated cells.

- The results indicate that in this mouse strain, a single immunization of either 10e9vp or 10e10vp of C7 Ade2 induce C-term and N-term specific CD4 and CD8 T cell
 40 responses (Figures 17 to 20). In particular, the intensity of the average observed response is equal if not higher when the 10e9 vp dose is used. The CS-specific CD8 T cell responses are mainly N term-specific while the CS-specific CD4 T cell responses are equally targeting the N-term and C-term region of the CS protein.

- 45 The cytokine profile of the CS-specific CD4 and CD8 T cell response was also determined and it was similar across all the tested timepoints. The profile displayed on d28 post-immunization is shown in Figures 21 to 24 and is representative of the other tested timepoints. Briefly, the CS-specific CD8 T cell responses are mostly composed of CD8 T cells producing IFN γ only (Figures 21 & 22). The CS-specific
 50 CD4 T cell responses are also composed of IFN γ producing CD4 T cells but also and to a lesser extent of CD4 T cells producing IL2 only or both IL2 & IFN γ (Figures 23 & 24).

5 Example 4

Immunogenicity of the C7-Ade2 in prime/boost or co-formulation with RTS,S/AS01B in CB6F1 mice

10 We have tested the immunogenicity of the C7 chimpadenovirus expressing the Ade2 construct in either prime-boost or co-formulation (combo) with RTS,S/AS01B in CB6F1 mice (4 pools of mice/group). AS01B is an adjuvant system containing 3D-MPL and QS21 formulated with liposomes. Mice were immunized intramuscularly on d0, 14 and 28 as follows:

	d0	d14	d28
Group 1	A	P	P
Group 2	P	P	A
Group 3	P	P	P
15 Group 4	C	C	C

Where,

A = 10e9 vp of C7 Ade2

P = 5µg RTS,S/50µl AS01B

20 C = 10e10 vp of C7 Ade2 + 5µg RTS,S/50µl AS01B

Peripheral blood was collected and pooled on days 21 (7d pII), 35 (7d pIII), 49(21d pIII), 63 (35d pIII), 77 (49d pIII) post-immunization and the CS C-term, CS N-term and HBs specific CD4 & CD8 T cell responses producing IL-2 and/or IFN-gamma were measured by flow cytometry, after overnight in vitro restimulation with pools of 15mer peptides covering the sequences of interest (CS N-term, CS C-term or HBs). As negative controls, some cells were also cultured overnight in vitro in culture medium (unstimulated). The Ag-specific responses were calculated by subtracting the average cytokine response produced by unstimulated cells from the average cytokine response produced by the peptide-stimulated cells.

The results indicate that:

- APP, PPA and CCC all induce N-term specific CD8 T cell responses. At the 7d pII timepoint, N-term specific CD8 T cell responses are observed in the CCC group, followed by the APP group. At the later timepoints tested, (21d pIII, 35d pIII & 49d pIII), these response are & remain of similar intensity in the APP, PPA and CCC groups (Figure 25).
- APP, PPA and CCC induce C-term specific CD8 T cell responses that still persist 49 days post 3rd immunization (Figure 26)
- N-term specific CD4 T cell responses are mainly detected in mice immunized with APP or CCC with higher intensities of such responses in the APP group (Figure 27)
- All groups display C-term specific CD4 T cell responses. However, APP and CCC induce similar higher levels of C-term specific CD4 T cell responses and these about 2 to 3 times higher than the ones induced by PPA and PPP at all the timepoints tested (Figure 28).
- The HBs-specific CD4 and CD8T cell responses are higher in the animals immunized with PPP than with APP, PPA or CCC (Figures 29 and 30).

- 5 - The CCC treatment regimen is the only one that is associated with the simultaneous induction of CS and HBs-specific CD4 and CD8 T cell responses.

10 The cytokine profiles of the CS- and HBs- specific CD4 and CD8 T cell responses were also determined and were similar across the timepoints tested. The ones from the 21d pIII timepoint are shown below as representative of all timepoints tested (Figures 31 to 36). Briefly, the Ag-specific CD8 T cell responses are mostly composed of CD8 T cells producing IFN γ (Figures 31 to 33). In contrast, the Ag-specific CD4 T cell responses are composed of a mixture of CD4 T cells producing IFN γ , IFN γ and IL-2 and to a lesser extent CD4 T cells producing IL-2 (Figures 34 to 36).

15 In addition, the Ag-specific antibody responses were determined by ELISA on sera collected 14 and 42 days post-3rd immunization. In particular, the total Ig responses against the R32LR polypeptide (i.e. which covers the middle portion of *P. falciparum* CSP) and against HBs were measured (Mettens et al., Vaccine 2008). All immunization regimens did elicit R32LR and HBs-specific antibody responses that persisted up to the last timepoint tested, i.e. 42 days post 3rd immunization (Figures 37 & 38).

25 Example 5

Immunogenicity of co-formulation C7-Ade2+ RTS,S/AS01B in CB6F1 mice

30 In this experiment, we compared the immunogenicity of the chimpanzadenovirus C7 Ade2 co-formulated (Combo) with RTS,S/AS01B. In particular, we compared the immune response elicited by 1, 2 or 3 injections of the combo in CB6F1 mice (4 pools of mice/group). In addition, different intervals between the 2 injections of the combo were evaluated (i.e. 14 & 21 days). Finally, a group of mice immunized with A-P-P served as control in the experiment. The experimental design can be summarized as follows:

35

		d0	d7	d14	d28
Group 1	C				C
Group 2	C-C (14d interval)			C	C
Group 3	C-C (21d interval)		C		C
Group 4	C-C-C	C		C	C
Group 5	A-P-P	A		P	P

Where,

A = 10e9 vp of C7 Ade2

40 P = 5 μ g RTS,S/50 μ l AS01B

C = 10e9 vp of C7 Ade2 + 5 μ g RTS,S/50 μ l AS01B

45 Peripheral blood was collected and pooled on days 35, 42, 49, 63 and 98 and the CS C-term, CS N-term and HBs specific CD4 & CD8 T cell responses producing IL-2 and/or IFN-gamma were measured by flow cytometry, after overnight in vitro restimulation with pools of 15mer peptides covering the sequences of interest, i.e. the N-terminal region (N-term), the C-terminal region (C-term) of the CS protein or HBs. As negative controls, some cells were also cultured overnight in vitro in culture medium (unstimulated). The Ag-specific responses were calculated by subtracting the

- 5 average cytokine response produced by unstimulated cells from the average cytokine response produced by the peptide-stimulated cells.

The results indicate that under these experimental conditions, 2 immunizations of the combo were required to simultaneously induce CS C-term, CS N-term and HBs-specific CD4 and CD8 T cell responses. The interval between the 2 immunizations of the combo did not seem to significantly impact the levels of Ag-specific T cell responses detected. There was a trend for higher HBs-specific CD4 and CD8 T cell responses in mice immunized 3 times with the combo. The kinetics of the Ag-specific T cell responses are shown in Figures 39 to 44.

15 The cytokine profiles of the CS- and HBs- specific CD4 and CD8 T cell responses were also determined and were similar across the timepoints tested. The ones from the day 42 of the study are shown below as representative of all timepoints tested (Figures 42 to 47). Briefly, the Ag-specific CD8 T cell responses are mostly composed of CD8 T cells producing IFN γ (Figures 45 to 47). In contrast, the Ag-specific CD4 T cell responses are composed of a mixture of CD4 T cells producing IFN γ , IFN γ and IL-2 and to a lesser extent CD4 T cells producing IL-2 (Figures 48 to 50).

25 In addition, the Ag-specific antibody responses were determined by ELISA on sera collected on day 56 and 99 of the study. In particular, the total Ig responses against the R32LR polypeptide (i.e. which covers the middle portion of *P. falciparum* CSP) and against HBs were measured (Mettens et al., Vaccine 2008). All immunization regimens did elicit R32LR and HBs-specific antibody responses: within each group, these responses were of similar intensity at both timepoints tested. In addition, when the groups immunized with the combo were compared, there was a trend for higher responses in groups immunized with 3 doses of the combo (Figures 51 & 52).

Example 6

35 **Evaluation of the need for each component of the combo, i.e. C7-Ade2, RTS,S and AS01B to elicit both CS & HBs T cell and Ab responses simultaneously in CB6F1 mice**

In this experiment, we evaluated the need for each component of the combo (i.e. C7 Ade2, RTS,S and AS01B) to elicit CS and HBs-specific CD4 and CD8 T cell responses simultaneously. In this experiment, CB6F1 mice (6 pools of mice/group) were immunized twice intramuscularly (on days 0 & 14) with the combo or components thereof as shown below:

	d0	d14
Group 1	C	C
Group 2	P	P
Group 3	RTS,S / buffer	RTS,S / buffer
Group 4	RTS,S / A / buffer	RTS,S / A / buffer
Group 5	A	A
Group 6	A / AS01B	A / AS01B
Group 7	RTS,S / C7 empty / AS01B	RTS,S / C7 empty / AS01B
Group 8	RTS,S / C7 empty / buffer	RTS,S / C7 empty / buffer

45 Where:

5

A = 10e9 vp of C7 Ade2

P = 5µg RTS,S/50µl AS01B

C = 10e9 vp of C7 Ade2 + 5µg RTS,S/50µl AS01B

C7 empty = 10e9 vp of C7 empty vector (no insert)

10

RTS,S = 5µg of RTS,S

AS01B = GSK Proprietary Adjuvant System 1B

Buffer = AS01B buffer (no immunostimulant)

Peripheral blood was collected and pooled on days 14, 28, 70, 91 & 112 and the CS C-term, CS N-term and HBs specific CD4 & CD8 T cell responses producing IL-2 and/or IFN-gamma were measured by flow cytometry, after overnight in vitro restimulation with pools of 15mer peptides covering the sequences of interest, i.e. the N-terminal region (N-term), the C-terminal region (C-term) of the CS protein or HBs. As negative controls, some cells were also cultured overnight in vitro in culture medium (unstimulated). The Ag-specific responses were calculated by subtracting the average cytokine response produced by unstimulated cells from the average cytokine response produced by the peptide-stimulated cells.

In addition, the Ag-specific antibody responses were determined by ELISA on sera collected on day 42 and 84 of the study. In particular, the total Ig responses against the R32LR polypeptide (i.e. which covers the middle portion of *P. falciparum* CSP) and against HBs were measured (Mettens et al., Vaccine 2008).

The results indicate that each component of the combo is required to simultaneously elicit CS (N-term & C-term) CD4 and CD8 T cell responses (Figures 53 to 58) as well as R32LR and HBs antibody responses (Figures 65 and 66).

The average cytokine profiles of the CS- and HBs- specific CD4 and CD8 T cell responses were also determined at each timepoint of the study and these are shown in Figures 59 to 64. Briefly, the Ag-specific CD8 T cell responses are mostly composed of CD8 T cells producing IFNγ (Figures 59 to 61). In contrast, the Ag-specific CD4 T cell responses are composed of a mixture of CD4 T cells producing IFNγ, IFNγ and IL-2 and to a lesser extent CD4 T cells producing IL-2 (Figures 62 to 64).

40

Example 7

Immunogenicity of a synthetic C7 Ade2 in CB6F1 mice

A synthetic C7 chimpadenovirus expressing the Ade2 construct was made available and its immunogenicity in mice was compared to the one of the original C7 Ade2. In this experiment, CB6F1 mice (6 pools of mice/group) were immunized with 10e9 vp of the original C7 Ade2 or its synthetic counterpart.

Peripheral blood was collected and pooled on days 21, 28 & 35 post-immunization and the CS C-term and CS N-term CD4 & CD8 T cell responses producing IL-2 and/or IFN-gamma were measured by flow cytometry, after overnight in vitro restimulation with pools of 15mer peptides covering the sequences of interest, i.e. the N-terminal region (N-term), the C-terminal region (C-term) of the CS protein. As negative controls, some cells were also cultured overnight in vitro in culture medium (unstimulated). The Ag-specific responses were calculated by subtracting the average

- 5 cytokine response produced by unstimulated cells from the average cytokine response produced by the peptide-stimulated cells.

10 The results indicate that both C7 adenoviruses elicited similar levels of N-term and C-term specific CD4 and CD8 T cell responses. In particular, and regardless of the viral vector used (original or synthetic), the Ag-specific CD8 T cell responses were mainly N-term specific (Figures 67 and 68). The N-term and C-term specific CD4 T cell responses were of similar intensity regardless of the viral vector used (Figures 69 and 70).

15 The cytokine profiles of the CS-specific CD4 and CD8 T cell responses were also determined and are shown in Figures 71 to 74. Briefly, the Ag-specific CD8 T cell responses were mostly composed of CD8 T cells producing IFN γ (Figures 71 & 72). In contrast, the Ag-specific CD4 T cell responses were composed of a mixture of CD4 T cells producing IFN γ , IFN γ and IL-2 and to a lesser extent CD4 T cells producing IL-2 (Figures 73 to 74).

SEQ ID NO 1**Amino acid sequence**

MMRKLA ILSVSSFLFVEALFQEYQCYGSSSNTRVLNELNYDNAGTNLYNE	50
LEMNYYGKQENWYSLKKNRSRLGENDDGNNNNGDNGREGKDEDKRDGNNE	100
DNEKLRKPKHKKLKQPADGNPDPNANPNVDPNANPNVDPNANPNVDPNAN	150
PNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNVDPNANPN	200
ANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNAN	250
PNANPNANPNANPNANPNKNNQGNGQGHNMPNDPNRNVDENANANSVKN	300
NNNEEPSDKHIKEYLNKIQNSLSTEWSPCSVTCGNGIQVRIKPGSANKPK	350
DELDYANDIEKKICKMEKCSSVFNVVNSAIGL	382

SEQ ID NO 2**Nucleotide sequence**

ATGATGAGAAAACCTTGCCATCCTCAGCGTCAGCTCTTTCCTGTTTCGTGGA	50
GGCCCTCTTCCAGGAGTATCAGTGCTACGGAAGCAGCAGCAATACAAGGG	100
TCCTGAACGAGCTCAACTATGACAACGCTGGAACGAACCTGTATAACGAG	150
CTGGAGATGAACTACTATGGCAAGCAGGAGAACTGGTATAGCCTGAAGAA	200
GAACAGCCCGGTCCCTGGGCGGAGAACGACGACGGCAACAACAACACGGCG	250
ACAACGGCAGGGAGGGCAAAGATGAGGACAAGAGGGACGGGAACAACGAG	300
GATAACGAGAAGCTGCGGAAGCCCAAGCACAAGAACTCAAGCAGCCCGC	350
CGACGGGAACCCGGACCCCAATGCAAATCCCAACGTCGACCCAAACGCAA	400
ACCCTAACGTGGACCCCAACGCCAATCCCAACGTCGATCCTAATGCCAAT	450
CCAAATGCCAACCCCTAACGCAAATCCTAATGCAAACCCCAACGCCAATCC	500
TAACGCCAACCCCAAATGCCAACCCCAAACGCTAACCCCAACGCTAACCCAA	550
ATGCAAATCCCAATGCTAACCCCAAACGTGGACCCTAACGCTAACCCCAAAC	600
GCAAACCCTAACGCCAATCCTAACGCAAACCCCAATGCAAACCCCAAACGC	650
AAATCCCAACGCTAACCCCTAACGCAAACCCCAACGCCAACCCCTAATGCCA	700
ACCCCAATGCTAACCCCAACGCCAATCCAAACGCAAATCCAAACGCCAAC	750
CCAAATGCAAACCCCAACGCTAATCCCAACGCCAACCCCAAACGCCAATCC	800
TAACAAGAACAATCAGGGCAACGGGCAGGGCCATAACATGCCGAACGACC	850
CTAATCGGAATGTGGACGAGAACGCCAACGCCAACAGCGCCGTGAAGAAC	900
AACAACAACGAGGAGCCCTCCGACAAGCACATCAAGGAATACCTGAACAA	950
GATCCAGAACAGTCTGAGCACCGAGTGGTCCCCCTGCTCCGTGACCTGCG	1000
GCAACGGCATCCAGGTGAGGATCAAGCCCGGCTCCGCCAACAAGCCCAAG	1050
GACGAGCTGGACTACGCCAACGACATCGAGAAGAAGATCTGCAAGATGGA	1100
GAAATGCAGCTCTGTGTTCAACGTCGTGAACTCCGCCATCGGCCTGTGA	1149

Seq ID NO 3

MMRKLAILSVSSFLFVEALFQEYQCYGSSSNTRVLNELNYDNAGTNLYNE	50
LEMNYYGKQENWYSLKKNSRSLGENDDGNNNNGDNGREGKDEDKRDGNNE	100
DNEKLRKPKHKKLKQPADGNPDPNANPNVDPNANPNVDPNANPNVDPNAN	150
PNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNVDPNANPN	200
ANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNAN	250
PNANPNANPNANKNNQGNGQGHNMPPNDPNRNVDENANANSVKNNNNEEP	300
SDKHIKEYLNKIQNSLSTEWSPCSVTCGNGIQVRIKPGSANKPKDELDDYA	350
NDIEKKICKMEKCSSVFNVVNS	372

Seq ID NO 4

Atgatgaggaaactggccatcctgagcgtgagcagcttcctgttcgtgga	50
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Tgtctgaacgagctgaactacgacaacgcggcaccaacctgtacaacgag	150
Ctggagatgaactactacggcaagcaggagaactggtacagcctgaagaa	200
Gaacagccggtctctctgggcgagaacgacgacggcaacaacaacaacggcg	250
Acaacggccgggagggaaggacgaggacaagcgggacggcaacaacgag	300
Gacaacgagaagctgcggaagcccaagcacaagaaacttaagcagccgc	350
Cgacggcaacccccgaccccaacgccaacccccaacgtggaccccaacgcca	400
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Cctaacgctaaccaccaatgccaacccaaatgccaatccaaatgcaaattcc	500
Caacgccaatccaaacgcaaaccctaattgctaattccaaacgctaattccta	550
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Gctaaccctaaacgcaaattcccaacgctaaccctgaacgcaaaccctaacgc	650
Caatccgaatgccaacccaaacgccaacccgaacgctaattccgaatgcta	700
Acccgaatgctaattcctaacgcaaaccctaaatgcaaaccctaatgcaaac	750
Ccgaacgccaatcccaacgccaatcctaattgccaacaagaacaatcaggg	800
Caacggccaggggccacaacatgcccaacgaccccaaccggaacgtggacg	850
Agaacgccaacgccaacagcgccgtgaagaacaacaacaacgaggagccc	900
Agcgacaagcacatcaaggagtacctgaacaagatccagaacagcctgag	950
Caccgagtggagcccctgcagcgtgacctgcggcaacggcattcaggtgc	1000
Ggatcaagcccggcagcgccaacaagcccaaggacgagctggactacgcc	1050
Aatgacatcgagaagaagatctgcaagatggagaagtgcagcagcgtgtt	1100
Caacgtggtgaactcctga	1119

Seq ID No. 5

Chimp Adeno 7 (seq ID No 17 from WO 03/046124)

Ala	Pro	Lys	Gly	Ala	Pro	Asn	Thr	Cys	Gln	Trp	Thr	Tyr	Lys	Ala	Gly
1			5					10					15		
Asp	Thr	Asp	Thr	Glu	Lys	Thr	Tyr	Thr	Tyr	Gly	Asn	Ala	Pro	Val	Gln
		20					25					30			
Gly	Ile	Ser	Ile	Thr	Lys	Asp	Gly	Ile	Gln	Leu	Gly	Thr	Asp	Ser	Asp
		35				40					45				
Gly	Gln	Ala	Ile	Tyr	Ala	Asp	Glu	Thr	Tyr	Gln	Pro	Glu	Pro	Gln	Val
	50					55				60					
Gly	Asp	Ala	Glu	Trp	His	Asp	Ile	Thr	Gly	Thr	Asp	Glu	Lys	Tyr	Gly
65					70				75					80	
Gly	Arg	Ala	Leu	Lys	Pro	Asp	Thr	Lys	Met	Lys	Pro	Cys	Tyr	Gly	Ser
			85					90						95	

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Phe Ala Lys Pro Thr Asn Lys Glu Gly Gly Gln Ala Asn Val Lys Thr
      100                      105                      110
Glu Thr Gly Gly Thr Lys Glu Tyr Asp Ile Asp Met Ala Phe Phe Asp
      115                      120                      125
Asn Arg Ser Ala Ala Ala Ala Gly Leu Ala Pro Glu Ile Val Leu Tyr
      130                      135                      140
Thr Glu Asn Val Asp Leu Glu Thr Pro Asp Thr His Ile Val Tyr Lys
      145                      150                      155                      160
Ala Gly Thr Asp Asp Ser Ser Ser Ser Ile Asn Leu Gly Gln Gln Ser
      165                      170                      175
Met Pro Asn Arg Pro Asn Tyr Ile Gly Phe Arg Asp Asn Phe Ile Gly
      180                      185                      190
Leu Met Tyr Tyr Asn Ser Thr Gly Asn Met Gly Val Leu Ala Gly Gln
      195                      200                      205
Ala Ser Gln Leu Asn Ala Val Val Asp Leu Gln Asp Arg Asn Thr Glu
      210                      215                      220
Leu Ser Tyr Gln Leu Leu Leu Asp Ser Leu Gly Asp Arg Thr Arg Tyr
      225                      230                      235                      240
Phe Ser Met Trp Asn Gln Ala Val Asp Ser Tyr Asp Pro Asp Val Arg
      245                      250                      255
Ile Ile Glu Asn His Gly Val Glu Asp Glu Leu Pro Asn Tyr Cys Phe
      260                      265                      270
Pro Leu Asp Ala Val Gly Arg Thr Asp Thr Tyr Gln Gly Ile Lys Ala
      275                      280                      285
Asn Gly Asp Asn Gln Thr Thr Trp Thr Lys Asp Asp Thr Val Asn Asp
      290                      295                      300
Ala Asn Glu Leu Gly Lys Gly Asn Pro Phe
      305                      310

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Seq ID No. 6

Chimp Adeno 7 (seq ID No 20 from WO 03/046124)

```

Thr Leu Trp Thr Thr Ala Asp Pro Ser Pro Asn Cys Lys Ile Tyr Ser
1      5      10
Glu Lys Asp Ala Lys Leu Thr Leu Cys Leu Thr Lys Cys Gly Ser Gln
      20      25      30
Ile Leu Gly Thr Val Thr Val Leu Ala Val Asn Asn Gly Ser Leu Asn
      35      40      45
Pro Ile Thr Asn Thr Val Ser Thr Ala Leu Val Ser Leu Lys Phe Asp
      50      55      60
Ala Ser Gly Val Leu Leu Ser Ser Ser Thr Leu Asp Lys Glu Tyr Trp
      65      70      75      80
Asn Phe Arg Lys Gly Asp Val Thr Pro Ala Glu Pro Tyr Thr Asn Ala
      85      90      95
Ile Gly Phe Met Pro Asn Ile Lys Ala Tyr Pro Lys Asn Thr Ser Ala
      100     105     110
Ala Ser Lys Ser His Ile Val Ser Gln Val Tyr Leu Asn Gly Asp Glu
      115     120     125
Ala Lys Pro Leu Met Leu Ile Ile Thr Phe Asn Glu Thr Glu Asp Ala
      130     135     140
Thr Cys Thr Tyr Ser Ile Thr Phe Gln Trp Lys Trp Asp Ser Thr Lys
      145     150     155     160
Tyr Thr Gly Glu Thr Leu Ala Thr Ser Ser Phe Thr Phe Ser Tyr Ile
      165     170     175
Ala Gln Glu

```

NNGDNGREGKDEDKRDGNN
AIGL

[Seq ID No: 7]
[Seq ID No: 8]

PNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNVDPN
 ANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNANPNAN
 PNANPNANPNANPNANPNANPNANPN

[Seq ID No: 9]

NANP NVDP NANP NVDP NANP NVDP NANP NANP NANP NANP
 NANP NANP NANP NANP NANP NANP NANP NVDP NANP NANP
 NANP NANP NANP NANP NANP NANP NANP NANP NANP NANP
 NANP NANP NANP NANP NANP NANP

[Seq ID No: 10]

TCC ATG ACG TTC CTG ACG TT (CpG 1826)

[Seq ID No: 11]

TCT CCC AGC GTG CGC CAT (CpG 1758)

[Seq ID No: 12]

ACC GAT GAC GTC GCC GGT GAC GGC ACC ACG

[Seq ID No: 13]

TCG TCG TTT TGT CGT TTT GTC GTT (CpG 2006)

[Seq ID No: 14]

TCC ATG ACG TTC CTG ATG CT (CpG 1668)

[Seq ID No: 15]

TCG ACG TTT TCG GCG CGC GCC G (CpG 5456),

[Seq ID No: 16]

Seq ID No: 17

Sequence of a expression cassette for a protein of Seq ID No. 3. The protein encoding region is underlined.

TA ACTATAACGGTCCTAAGGTAGCGAAAGCTCAGATCGGCTGACCGCCCAACGACCC
 CCGCCCATTTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTT
 CCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCA
 AGTGTATCATATGCCAAGTCCGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC
 CTGGCATTATGCCCAGTACATGACCTTACGGGACTTTCCCTACTTGGCAGTACATCTA
 CGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACACCAATGGGCG
 TGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTTGACGTCAATGG
 GAGTTTGT TTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAATAACCCCGC
 CCCGTTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGC
 TCGTTTAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCA
 TAGAAGACACCGGGACCGATCCAGCCTCCGCGGCCGGGAACGGTGCATTGGAACGCG
 GATTCCCCGTGCCAAGAGTGCGGCCAGCTTTATTGCGGTAGTTTATCACAGTTAAAT
 TGCTAACGCAGTCAGTGCTTCTGACACAACAGTCTCGAACTTAAGCTGCAGAAGTTG
 GTCGTGAGGCACTGGGCAGGTAAGTATCAAGGTTACAAGACAGGTTTAAGGAGACCA
 ATAGAACTGGGCTTGTCGAGACAGAGAAGACTCTTGCGTTTCTGATAGGCACCTAT
 TGGTCTTACTGACATCCACTTTGCCTTTCTCTCCACAGGTGTCCACTCCCAGTTCAA
 TTACAGCTCTTAAGGCTAGAGTGGCCGCACCATGATGAGGAACTGGCCATCCTGAG
CGTGAGCAGCTTCCTGTTTCGTGGAGGCCCTGTTTCAGGAGTACCAGTGCTACGGCAG
CAGCAGCAACACCCGGGTGCTGAACGAGCTGAACTACGACAACGCCGGCACCAACCT
GTACAACGAGCTGGAGATGAACTACTACGGCAAGCAGGAGAACTGGTACAGCCTGAA
GAAGAACAGCCGGTCTCTGGGCGAGAACGACGACGGCAACAACAACAGGCGACAA
CGGCCGGGAGGGCAAGGACGAGGACAAGCGGGACGGCAACAACGAGGACAACGAGAA
GCTGCGGAAGCCCAAGCACAAAGAACTTAAGCAGCCCGCCGACGGCAACCCCGACCC
CAACGCCAACCCCAACGTGGACCCCAACGCCAATCCTAATGTCGACCCCAATGCCAA
TCCGAACGTTGATCCCAATGCGAATCCTAACGCTAACCCCAATGCCAACCCCAATGC
CAATCCAAATGCAAATCCCAACGCCAATCCAAACGCAAACCCTAATGCTAATCCAAA
CGCTAATCCTAATGCCAATCCCAATGCTAACCCAAACGTCGATCCTAACGCAAATCC
GAACGCTAACCCCAACGCAAATCCCAACGCTAACCCGAACGCAAACCCTAACGCCAA
TCCGAATGCCAACCCCAACGCCAACCCGAACGCTAATCCGAATGCTAACCCGAATGC
TAATCCTAACGCAAACCCCAATGCAAACCCCAATGCAAACCCGAACGCCAATCCCAA

CGCCAATCCTAATGCCAACAAGAACAATCAGGGCAACGGCCAGGGCCACAACATGCC
 CAACGACCCCAACCGGAACGTGGACGAGAACGCCAACGCCAACAGCGCCGTGAAGAA
 CAACAACAACGAGGAGCCCAGCGACAAGCACATCAAGGAGTACCTGAACAAGATCCA
 GAACAGCCTGAGCACCGAGTGGAGCCCCTGCAGCGTGACCTGCGGCAACGGCATTCA
 GGTGCGGATCAAGCCCGGCAGCGCCAACAAGCCCAAGGACGAGCTGGACTACGCCAA
 TGACATCGAGAAGAAGATCTGCAAGATGGAGAAGTGCAGCAGCGTGTTCAACGTGGT
 GAACTCCTGAGGATCCGATCTTTTTCCCTCTGCCAAAAATTATGGGGACATCATGAA
 GCCCCTTGAGCATCTGACTTCTGGCTAATAAAGGAAATTTATTTTCATTGCAATAGT
 GTGTTGGAATTTTTTGTGTCTCTCACTCGGAAGCGATCTGAATTCATCTATGTCGGG
 TGCGGAGAAAGAGGTAATGAAATGGCA

Seq ID No: 18

Sequence of Ade2 expression cassette is below. The protein encoding region is underlined.

TAATAACGGTCCTAAGGTAGCGAAAGCTCAGATCGGCTGACCGCCCAACGACCC
 CCGCCCATTTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTT
 CCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCA
 AGTGTATCATATGCCAAGTCCGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGC
 CTGGCATTATGCCCAGTACATGACCTTACGGGACTTTCCCTACTTGGCAGTACATCTA
 CGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACACCAATGGGCG
 TGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTTGACGTCAATGG
 GAGTTTGTGTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAATAACCCCGC
 CCCGTTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGC
 TCGTTTAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCA
 TAGAAGACACCGGGACCGATCCAGCCTCCGCGGCGGGGAACGGTGCATTGGAACGCG
 GATTCCCCGTGCCAAGAGTGCGGCCAGCTTTATTGCGGTAGTTTATCACAGTTAAAT
 TGCTAACGCAGTCAGTGCTTCTGACACAACAGTCTCGAACTTAAGCTGCAGAAGTTG
 GTCGTGAGGCACTGGGCAGGTAAGTATCAAGGTTACAAGACAGGTTTAAGGAGACCA
 ATAGAACTGGGCTTGTCGAGACAGAGAAGACTCTTGCGTTTCTGATAGGCACCTAT
 TGGTCTTACTGACATCCACTTTGCCTTTCTCTCCACAGGTGTCCACTCCCAGTTCAA
 TTACAGCTCTTAAGGCTAGAGTGGCCGCACCATGATGAGAAAACCTGCCATCCTCAG
CGTCAGCTCTTTCCTGTTTCGTGGAGGCCCTCTTCCAGGAGTATCAGTGCTACGGAAG
CAGCAGCAATACAAGGGTCCTGAACGAGCTCAACTATGACAACGCTGGAACGAACCT
GTATAACGAGCTGGAGATGAACTACTATGGCAAGCAGGAGAAGTGGTATAGCCTGAA
GAAGAACAGCCGGTCCCTGGGCGGAGAACGACGACGGCAACAACAACGCGGACAA
CGGCAGGGAGGGCAAAGATGAGGACAAGAGGGACGGGAACAACGAGGATAACGAGAA
GCTGCGGAAGCCCAAGCACAAAGAACTCAAGCAGCCCGCCGACGGGAACCCGGACCC
CAATGCAAATCCCAACGTGACCCCAAACGCAAACCCCTAACGTGGACCCCAACGCCAA
TCCCAACGTCGATCCTAATGCCAATCCAAATGCCAACCCTAACGCAAATCCTAATGC
AAACCCCAACGCCAATCCTAACGCCAACCCTAACGCAAACCCAAACGCTAACCCCAA
CGCTAACCCCAAATGCAAATCCCAATGCTAACCCCAAACGTGGACCCCTAACGCTAACCC
CAACGCAAACCCCTAACGCCAATCCTAACGCAAACCCCAATGCAAACCCCAAACGCAA
TCCCAACGCTAACCCCTAACGCAAACCCCAACGCCAACCCTAATGCCAACCCCAATGC
TAACCCCAACGCCAATCCAAACGCAAATCCAAACGCCAACCCTAATGCAAACCCCAA
CGCTAATCCCAACGCCAACCCTAACGCCAATCCTAACAAAGAACAATCAGGGCAACGG
GCAGGGCCATAACATGCCGAACGACCCTAACCGGAATGTGGACGAGAACGCCAACGC
CAACAGCGCCGTGAAGAACAACAACGAGGAGCCCTCCGACAAGCACATCAAGGA
ATACCTGAACAAGATCCAGAACAGTCTGAGCACCGAGTGGTCCCCCTGCTCCGTGAC
CTGCGGCAACGGCATCCAGGTGAGGATCAAGCCCGGCTCCGCCAACAAGCCCAAGGA

CGAGCTGGACTACGCCAACGACATCGAGAAGAAGATCTGCAAGATGGAGAAATGCAG
CTCTGTGTTCAACGTCGTGAACTCCGCCATCGGCCTGTGAGGATCCGATCTTTTCC
CTCTGCCAAAAATTATGGGGACATCATGAAGCCCCTTGAGCATCTGACTTCTGGCTA
ATAAAGGAAATTTATTTTCATTGCAATAGTGTGTTGGAATTTTTTGTGTCTCTCACT
CGGAAGCGATCTGAATTCATCTATGTCGGGTGCGGAGAAAGAGGTAATGAAATGGCA
T

Claims

1. A replication deficient simian adenoviral vector C7 encoding a protein comprising CS protein from *P. falciparum* or a fragment thereof.
2. A viral vector according to claim 1, wherein the protein encoded comprises the sequence of Seq ID No: 7.
3. A viral vector according to claim 1 or claim 2, where the protein encoded comprises the sequence of Seq ID No: 8.
4. A viral vector according to any one of claims 1 to 3, wherein the protein encoded has the sequence of Seq ID No: 1.
5. A viral vector according to claim 1 or claim 2, wherein the protein encoded has the sequence of Seq ID No: 3.
6. A composition comprising a viral vector as defined in any one of claims 1 to 5 and an excipient.
7. A vaccine composition for the treatment or prophylaxis of malaria comprising a viral vector as defined in any one of claims 1 to 5 and an adjuvant.
8. A vaccine as defined in claim 7, which further comprises a protein.
9. A vaccine as defined in claim 8, wherein the protein is RTS,S.
10. A vaccine composition comprising (1) a replication deficient simian adenoviral vector C7 encoding a protein comprising CS protein from *P. falciparum* or a fragment thereof (2) a malaria antigen, and (3) an adjuvant.
11. A kit comprising (1) a replication deficient simian adenoviral vector C7 encoding a protein comprising CS protein from *P. falciparum* or a fragment thereof (2) a malaria antigen, and (3) an adjuvant.
12. A vaccine or kit as claimed in claim 10 or claim 11, wherein the protein encoded by the adenoviral vector C7 has the sequence of Seq ID No: 1.
13. A vaccine or kit as claimed in any of claims 7 to 12, wherein the malaria antigen is RTS,S.
14. A vaccine or kit according to any of claims 7 to 13, wherein the adjuvant comprises 3D-MPL.
15. A vaccine or kit according to any of claims 7 to 13, wherein the adjuvant comprises a saponin.
16. A vaccine or kit according to claim 15, wherein the saponin is QS21.

17. A vaccine or kit according to any of claims 7 to 13, wherein the adjuvant comprises 3D-MPL and QS21.
18. A vaccine or kit as defined in any one of claims 7 to 17, wherein the formulation is provided as an oil-in-water emulsion.
19. A vaccine as defined in any one of claims 7 to 10 or 12 to 17, wherein the vaccine is a liposomal formulation.
20. A vaccine composition as claimed in claim 10 comprising (1) a replication deficient simian adenoviral vector C7 encoding a protein comprising CS protein from *P. falciparum* having the sequence of Seq ID No: 1 (2) malaria antigen RTS,S, and (3) an adjuvant comprising 3D-MPL and QS21.
21. A process for the preparation of a viral vector as defined in any one of claims 1 to 5 comprising the steps of:
 - a. propagating the vector on a suitable cell line, and
 - b. recovering the vector.
22. A process for the preparation of a composition of claim 6 or a vaccine as defined in any one of claims 7 to 10 or 12 to 20 comprising the step of admixing the viral vector of claims 1 to 5 with at least one excipient/carrier.
23. A viral vector as defined in any one of claims 1 to 5, for the treatment or prophylaxis of malaria.
24. A viral vector as claimed in any of claims 1 to 5 for priming or boosting in a prime boost regime for the treatment or prophylaxis of malaria.
25. Use of a viral vector as defined in any one of claims 1 to 5 in the manufacture of a medicament for the treatment or prophylaxis of malaria.
26. A method of treatment comprising administering a therapeutically effective amount of:
 - a. a viral vector as defined in any one of claims 1 to 5,
 - b. a composition as defined in claim 6, or
 - c. a vaccine as defined in any one of claims 7 to 10 or 12 to 20.