

DESCRIPTION

BACULOVIRAL VECTORS WITH A DUAL VERTEBRATE AND BACULOVIRUS
PROMOTER CONTROLLING AN IMMUNOGENIC FUSION GENE

TECHNICAL FIELD

5 The present invention provides a novel transfer vector,
a recombinant baculovirus obtained by homologous recombination of
the transfer vector and a baculovirus DNA, and methods for
production thereof.

10 The present invention further provides pharmaceuticals
(e.g., vaccines, and preventive or therapeutic drugs for
infectious diseases such as malaria and influenza) containing the
recombinant baculovirus as an active ingredient.

BACKGROUND ART

15 Baculovirus has been used as a vector in methods of
industrially producing a desired protein using insect cells. In
recent years, it has been found that baculovirus can introduce a
foreign gene not only into insect cells but also into mammalian
cells, and the possibility of their use as a vector for
introducing a therapeutic gene has been found. Patent Document 1
20 discloses a recombinant baculovirus expression vector containing
multiple independent promoters comprising a promoter derived from
an early gene of baculovirus, which has a DNA region containing a
gene encoding a viral non-structural protein, and a promoter
derived from a late gene of baculovirus, which has a DNA region
25 containing a gene encoding a viral structural protein.

30 Patent Document 2 discloses a method comprising
introducing into mammalian cells a non-mammalian DNA viral vector
containing multiple independent promoters controlled to express a
desired foreign gene linked to the promoters; and expressing the
foreign gene in the mammalian cells.

35 Further, Patent Document 3 discloses a method of
producing a protein with gene recombination technology using a
baculovirus. The method comprises expressing a fusion gene
obtained by linking the gp64 gene of baculovirus to a gene
encoding a desired protein to produce the desired protein in a

form fused with viral particles, collecting the viral particles fused with the desired protein, and cleaving the desired protein from the viral particles to collect the protein.

With respect to a baculovirus expression system, Patent Document 4 discloses a recombinant baculovirus expression vector having multiple independent promoters containing a first nucleic acid sequence encoding a detection marker, which is linked, in a form capable of functioning, to a first promoter that is active in host cells and inactive in non-acceptable cells, and a second nucleic acid sequence containing a foreign nucleic acid sequence, which is linked, in a form capable of functioning, to a second promoter that is active in non-acceptable cells.

Patent Document 5 discloses that an influenza virus hemagglutinin (HA) antigen-expressing recombinant baculovirus vector linked to a CAG promoter derived from chicken β actin has influenza virus infection-preventing effects and is therefore useful as a vaccine formulation.

Patent Document 6 discloses a method of producing a baculovirus vector comprising the step of co-transfecting into insect cells a plasmid containing a baculovirus promoter and a mammalian cell-derived promoter having linked thereto a gene encoding a protein expressible on the cell surface, or a plasmid containing two baculovirus promoters having linked thereto a gene encoding a protein expressible on the cell surface has been linked.

Patent Document 7 describes research on anti-influenza virus activity, i.e., activity against influenza virus infection, of a recombinant baculovirus having cDNA of influenza virus HA incorporated in a CAG promoter, and discloses that not only the recombinant baculovirus but also wild-type baculovirus have anti-influenza virus activity.

As shown above, various recombinant baculovirus vectors have been developed in recent years, and many attempts have been made to develop pharmaceuticals for mammals containing such a recombinant baculovirus vector as an active ingredient.

In this technical field, the development of pharmaceutical formulations, particularly vaccine formulations containing, as an active ingredient, a novel recombinant baculovirus, which is a recombinant baculovirus vector having a novel structure and being effective against malaria, influenza, tuberculosis, and like infectious diseases, or diseases such as cancer, has been desired.

Patent Document 1: Japanese Patent No. 3366328, Multiple Promoter Baculovirus Expression System and Defect Particle Products.

10 Patent Document 2: WO98/011243, Non-mammalian DNA Virus Having Modified Coating Protein.

Patent Document 3: JP No. 2002-235236-A, Methods of Producing Proteins.

Patent Document 4: JP No. 2003-284557-A, Novel Baculovirus-
15 Transfecting Vector and Recombinant Baculovirus for Expression of Foreign Gene.

Patent Document 5: WO02/062381, Baculovirus Vector Vaccine.

Patent Document 6: WO04/029259, Baculovirus Vector, Method of Producing Baculovirus Vector, and Method of Introducing Gene.

20 Patent Document 7: JP No. 2005-15346-A, Baculovirus-containing Anti-viral Agent.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the test results of the expression of vaccine antigens from recombinant baculoviruses of the present
25 invention in insect cells in Example 3.

Detected by gp64 Monoclonal Antibody (AcV5)

Lane 1: AcNPV-WT

Lane 2: AcNPV-CAP-PfCSP

Lane 3: AcNPV-CAP-HA1/Anhui

30 Lane 4: AcNPV-CAP-HA1/Vietnam

FIG. 2 (A) shows a Western blotting analysis showing the expression of the CSP gene (PfCSP) of human malaria in viral particles of recombinant baculoviruses produced from recombinant transfer vectors.

35 Detected by Anti-PfCSP Monoclonal Antibody (2A10)

Lane 1: AcNPV-CAP-PfCSP

Lane 2: AcNPV-CAP-PfCSP/272

Lane 3: AcNPV-CAP-PfCSP/467

FIG. 2 (B) shows a Western blotting analysis showing
5 the expression of H5N1/HA1 gene in viral particles of recombinant
baculoviruses produced from recombinant transfer vectors.

Detected by H5N1/Vietnam Rabbit Polyclonal Antibody (IT-003-005)

Lane 1: AcNPV-WT (Cell Lysate)

Lane 2: AcNPV-CAP-HA1/Anhui (Cell Lysate)

10 Lane 3: AcNPV-CAP-HA1/Vietnam (Cell Lysate)

Lane 4: AcNPV-WT (Virion)

Lane 5: AcNPV-CAP-HA1/Vietnam (Virion)

Lane 6: Purified H5N1/Anhui Antigen (IT-003-0053p)

FIG. 3 shows HepG2 cells stained with a fluorescence-
15 labeled antibody, which indicates that an antigen has been
expressed by a recombinant baculovirus containing a fusion gene
of PfMSP1 gene and PfCSP gene in the HepG2 cells. The results of
FIG. 3 (A) confirmed that a PfCSP antigen has been expressed. The
results of FIG. 3 (B) confirmed that a PfMSP-1₁₉ antigen has been
20 expressed.

FIG. 4 shows the results of measurement of antibody
titers obtained in Example 6.

FIG. 5 shows the transfer vectors of the present
invention.

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DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

An object of the present invention is to provide a
novel recombinant transfer vector, a recombinant baculovirus
obtained by homologous recombination of the recombinant transfer
30 vector and a baculovirus DNA, and methods for production thereof.
Another object of the present invention is to provide a
pharmaceutical preparation, particularly a vaccine formulation
containing the recombinant baculovirus as an active ingredient.

MEANS FOR SOLVING THE PROBLEMS

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The present inventors found a transfer vector having a

novel structure capable of expressing a fusion protein of a protein having a desired immunogenicity or a partial protein thereof with a viral structural protein in insect cells and in vertebrate (particularly mammalian and avian) cells; and a
5 recombinant baculovirus obtained by homologous recombination of the transfer vector and a baculovirus DNA. Using the obtained recombinant baculovirus, the present inventors carried out extensive research on pharmaceuticals containing as an active ingredient a recombinant baculovirus having infectious disease-
10 preventive and therapeutic effects. As a result, the inventors found that the obtained recombinant baculovirus has the desired pharmaceutical effects.

Thus, the inventors of the present invention found a recombinant transfer vector having a novel structure, a
15 recombinant baculovirus obtained by homologous recombination of the transfer vector and a baculovirus DNA, and methods for the production thereof, and ascertained that the recombinant baculovirus itself is useful as a pharmaceutical capable of expressing a protein having the desired immunogenicity in target
20 cells, and as a pharmaceutical for preventing infectious diseases such as malaria and influenza. The present invention has been accomplished, based on these findings.

The present invention provides the inventions shown in the following items 1 to 22:

- 25 Item 1. A transfer vector which is any one of pCAP-PfCSP, pCAP-PfCSP/272, pCAP-PfCSP/467, pCAP-PfCSP(A361E), pCAP-PfCSP(A361E)/272, pCAP-PfCSP(A361E)/467, pCAP-PfCSP-76, pCAP-PfCSP-76/467, pCAP-PfCSP+209, pCAP-PfCSP+209/467, pCAP-PfCSP+76/209, pCAP-PfCSP+76/209/467, pCAP-HA1/Anhui, pCAP-HA1/Anhui/272, pCAP-HA1/Anhui/467, pCAP-HA1/Vietnam, pCAP-HA1/Vietnam/51, pCAP-HA1/Vietnam/101, pCAP-HA1/Vietnam/154, pCAP-HA1/Vietnam/201, pCAP-HA1/Vietnam/272, pCAP-HA1/Vietnam/467, pCAP-AH/345, pCAP-AH/345/467, pCAP-AH/410, pCAP-AH/410/467, pCAP-AH/473, pCAP-AH/473/467, pCAP-AH/520, pCAP-AH/520/467, pCAP-VN/346, pCAP-VN/346/467, pCAP-VN/410, pCAP-VN/410/467, pCAP-
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- VN/473, pCAP-VN/473/467, pCAP-VN/520, pCAP-VN/520/467, pCAP-CO/full, pCAP-CO/full/467, pCAP-CO/19, pCAP-CO/19/467, pCAP-CO/76, pCAP-CO/76/467, pCAP-CO/205, pCAP-CO/205/467, pCA39-HA1/Anhui, pCA64-HA1/Anhui, pCA39-PfCSP(A361E), pCA64-PfCSP(A361E), pCAP-
- 5 CO/full/VSV, pCAP-CO/19/VSV, pCAP-CO/76/VSV, pCAP-CO/205/VSV, pDual-Pfs25-PfCSP-gp64, and pDual-PfMSP1-PfCSP-gp64.
- Item 2. A recombinant baculovirus which is any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-
- 10 PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101,
- 15 AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-
- 20 CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui,
- 25 AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64.
- Item 3. A composition for infectious diseases comprising the
- 30 recombinant baculovirus of item 2 as an active ingredient.
- Item 4. A composition for infectious diseases comprising the recombinant baculovirus of item 2 as an active ingredient, the composition being administered by the intramuscular, respiratory, or nasal route.
- 35 Item 5. A vaccine comprising the recombinant baculovirus of item

2 as an active ingredient.

Item 6. A vaccine comprising the recombinant baculovirus of item 3 as an active ingredient, the composition being administered by the intramuscular, respiratory, or nasal route.

- 5 Item 7. A therapeutic or preventive agent for influenza virus infection, comprising as an active ingredient any one of AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-
10 HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-
15 VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CA39-HA1/Anhui, and AcNPV-CA64-HA1/Anhui.

- Item 8. A therapeutic or preventive agent for influenza virus infection according to item 7, which is administered by the
20 intramuscular, respiratory, or nasal route.

- Item 9. A vaccine against influenza virus infection, comprising as an active ingredient any one of AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-
25 HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-
30 CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CA39-HA1/Anhui, and AcNPV-CA64-HA1/Anhui.

- Item 10. A vaccine against influenza virus infection according to item 7, which is administered by the intramuscular, respiratory,
35 or nasal route.

Item 11. A therapeutic or preventive agent for human malaria infection, comprising as an active ingredient any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64.

Item 12. A therapeutic or preventive agent for human malaria infection according to item 11, which is administered by the intramuscular, respiratory, or nasal route.

Item 13. A therapeutic or preventive agent for human malaria infection, comprising as an active ingredient any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64.

Item 14. A therapeutic or preventive agent for human malaria infection according to item 13, which is administered by the intramuscular, respiratory, or nasal route.

Item 15. A method of preventing malaria or influenza infection or of treating malaria or influenza, comprising administering to a subject an effective amount of the recombinant baculovirus of

item 2, the composition for infectious diseases of item 3 or 4, or the vaccine of item 5, 6, 9, 10, 13 or 14.

Item 16. A method according to item 15, wherein the recombinant baculovirus, composition, or vaccine is administered to the
5 subject as a liposomal formulation.

Item 17. A method according to item 15, wherein the recombinant baculovirus, composition, or vaccine is administered to the subject by the intramuscular, respiratory, or nasal route.

Item 18. A method according to item 16, wherein the recombinant
10 baculovirus, composition, or vaccine is administered to the subject by the intramuscular, respiratory, or nasal route.

Item 19. A method of immunostimulation comprising administering to a subject an effective amount of the recombinant baculovirus of item 2, the composition for infectious diseases of item 3 or 4,
15 or the vaccine of item 5, 6, 9, 10, 13 or 14.

Item 20. A method according to item 19, wherein the recombinant baculovirus, composition, or vaccine is administered to the subject as a liposomal formulation.

Item 21. A method according to item 19, wherein the recombinant
20 baculovirus, composition, or vaccine is administered to the subject by the intramuscular, respiratory, or nasal route.

Item 22. A method according to item 20, wherein the recombinant baculovirus, composition, or vaccine is administered to the subject by the intramuscular, respiratory, or nasal route.

25 EFFECT OF THE INVENTION

According to the present invention, a novel recombinant transfer vector, a recombinant baculovirus obtained by homologous recombination of the recombinant transfer vector and a baculovirus DNA, and methods for production thereof are
30 provided. Pharmaceuticals containing the recombinant baculovirus of the present invention as an active ingredient are useful as therapeutic or preventive drugs for infectious diseases such as malaria and influenza, or as cellular medicine and vaccine formulations.

35 BEST MODE FOR CARRYING OUT THE INVENTION

The abbreviations used for the amino acids, peptides, base sequences, and nucleic acids in the present specification are based on the abbreviations specified in the IUPAC-IUB Communication on Biochemical Nomenclature, Eur. J. Biochem., 138: 9 (1984) and "Guideline for Preparing Specifications Including Base Sequences and Amino Acid Sequences" (Patent Office), and those commonly used in this technical field. In the present specification, the DNA molecule may include not only double strand DNA but also single strand DNA, i.e., a sense chain and an antisense chain constituting the double strand DNA, and is not limited to a full length thereof. The polynucleotide (DNA molecule) encoding the immunogenic foreign gene of the present invention encompasses double strand DNA containing genomic DNA, single strand DNA (sense chain) containing cDNA, and single strand DNA (antisense chain) having a sequence complementary to the sense chain, synthetic DNA, and fragments thereof, unless otherwise mentioned.

The polynucleotide or DNA molecule used herein is not limited in the functional region, and may include at least one of an expression suppression region, a coding region, a leader sequence, an exon, and an intron.

Further, examples of the polynucleotide include RNA and DNA. The polypeptide containing a specific amino acid sequence and the polynucleotide containing a specific DNA sequence include fragments, homologs, derivatives, and mutants of the polynucleotide.

Examples of mutants of the polynucleotide, such as mutant DNA, include naturally occurring allelic mutants; artificial mutants; and mutants having deletion, substitution, addition, and/or insertion. However, it should be understood that such mutants encode polypeptides having substantially the same function as the polypeptide encoded by the original non-mutated polynucleotide.

In the present invention, the transfer vector refers to a plasmid for producing a recombinant baculovirus having a

structure in which a fusion gene, formed by linking at least one gene encoding a protein capable of being a component of viral particles to at least one immunogenic foreign gene, is incorporated downstream of a dual promoter comprising two linked
5 promoters, i.e., one vertebrate promoter (e.g., a mammalian promoter or an avian promoter) and one baculovirus promoter.

In one preferable embodiment of the invention, the immunogenic foreign gene is located downstream of the dual promoter and upstream of the gene encoding a protein capable of
10 being a component of viral particles. The recombinant baculovirus of the present invention is used as an active ingredient of pharmaceuticals or vaccines for vertebrates. Examples of vertebrates include mammals such as humans, cattle, horses, swine, sheep, goats, monkeys, mice, dogs, and cats. Examples of birds
15 include chickens, quail, geese, wild ducks, pigeons, turkeys, guinea fowls, and parrots.

In one embodiment, the present invention provides a transfer vector containing a novel structure having incorporated therein a fusion gene of one immunogenic foreign gene and a gene
20 encoding a viral membrane protein that can be expressed in insect cells under the control of a dual promoter comprising one vertebrate promoter and one baculovirus promoter linked to each other. Co-transfection of this transfer vector with a baculovirus DNA into insect cells induces a homologous recombination and
25 thereby produces a recombinant baculovirus having incorporated therein the fusion gene that is expressed under the control of a baculovirus promoter in insect cells and that can produce a fusion protein capable of being a component of budded viral particles.

30 In the present invention, when the recombinant baculovirus is administered to a vertebrate, a fusion protein of a protein capable of being a component of budded viral particles with an immunogenic protein seems to function as a component vaccine. Further, the recombinant baculovirus administered to the
35 vertebrate enters the vertebrate cell, and a fusion antigen with

the desired immunogenic foreign antigen is produced from the viral genome in the vertebrate cell, and functions as a DNA vaccine.

Thus, for example, when the recombinant baculovirus of
5 the present invention is administered to a mammal, a fusion protein of a protein capable of being a component of viral particles with an immunogenic protein is presented as an antigen on the surface of virus particles, and a fusion protein of a protein capable of being a component of viral particles with an
10 immunogenic protein is produced in the mammalian cell, and seems to function as a preventive or therapeutic agent for infectious diseases, such as viral, protozoan, and bacterial infection, due to its immunopotentiative action.

The baculovirus DNA to be co-transfected with the
15 transfer vector may be a wild type, mutant, or recombinant baculovirus DNA. Examples of host cells to be co-transfected include insect cells such as cells of *Spodoptera frugiperda*.

In the present invention, the immunogenic foreign gene refers to a gene encoding the amino acid sequence of an antigenic
20 protein used as an immunogen in immunotherapy, such as vaccine therapy, for the prevention and treatment of infectious diseases, such as malaria and influenza. Specific examples thereof include genes encoding the amino acid sequences of proteins, such as malaria antigen and influenza virus antigen.

25 The "foreign" gene as used herein refers to a gene introduced from the outside. Even if the same gene is present in the cell, the gene introduced from the outside is referred to as the "foreign" gene.

In the present invention, the gene encoding the amino
30 acid sequence of a protein used as the immunogen is not particularly limited, as long as the gene is capable of encoding the amino acid sequence of an antigenic protein having immunogenicity against a substance that causes diseases such as infectious diseases. Examples of genes encoding the amino acid
35 sequence of an antigenic protein having immunogenicity are as

follows.

Examples of genes encoding the amino acid sequence of a malaria antigen include genes encoding the amino acid sequences of sporozoite surface antigen CSP (Circumsporozoite Protein) of malaria parasites, merozoite surface membrane protein MSP1 (Merozoite Surface Protein 1), malaria S antigen secreted from erythrocytes infected with malaria, PfEMP1 protein present in the knobs of erythrocytes infected with malaria, SERA protein, TRAMP protein, AMA1 protein, and like proteins.

Examples of genes encoding the amino acid sequences of influenza virus antigens include genes encoding the amino acid sequences of HA antigen (hemagglutinin antigen), NA antigen (neuraminidase antigen), M2 antigen (matrix protein antigen), NP antigen (nucleoprotein antigen), and like proteins.

Of the vertebrate genes, examples of mammalian genes include genes encoding the amino acid sequences of antigenic proteins of infectious diseases in humans, cattle, horses, swine, sheep, monkeys, mice, dogs, and cats. Examples of avian genes include antigen genes (e.g., avian influenza HA antigen) of infectious diseases in chickens, wild ducks, pigeons, turkeys, guinea fowls, and parrots.

Pathogen genes whose association with infectious diseases in mammals and birds as mentioned above has been reported are easily available from institutions storing registered public data on pathogen genes, such as Genbank.

The present invention can provide a transfer vector having such an immunogenic foreign gene, and a recombinant baculovirus obtained by homologous recombination of the transfer vector. Further, the present invention can provide a pharmaceutical composition containing as an active ingredient the recombinant baculovirus having the immunogenic foreign gene, and a vaccine formulation of the pharmaceutical composition.

The baculovirus used in the present invention refers to insect pathogen viruses that cause infection in insects, which are one group (*Baculoviridae*) of DNA viruses having a cyclic

double strand DNA as a gene. Among these, one group of the viruses referred to as the nucleopolyhedrosis virus (NPV) produce an inclusion body, referred to as a polyhedron, in the nucleus of infected cells in the late phase of infection. Even if a foreign gene to be expressed is inserted in place of the polyhedrin gene, virus infection and growth sufficiently occur to produce a large amount of the desired foreign gene product. Therefore, this virus has been used for the production of desired proteins in recent years.

10 Examples of the baculovirus used in the present invention include *Autographa californica nucleopolyhedrosis* virus: AcNPV, *Bombyx mori nucleopolyhedrosis* virus: BmNPV, *Orgyia pseudotsugata nucleopolyhedrosis* virus: OpNPV, and *Lymantria disper nucleopolyhedrosis* virus: LdNPV.

15 The baculovirus DNA may be any DNA that can be homologously recombined with the transfer vector of the present invention. More specifically, the viral gene of the baculovirus DNA that can be homologously recombined with the transfer vector of the present invention is as huge as 130 kbp in size, and an immunogenic foreign gene of 15 kbp or more can be inserted therein. Because the baculovirus gene itself is scarcely expressed in vertebrate cells, there is almost no need to consider its cytotoxicity. Thus, it is thought that no harmful immune response is induced.

25 (1) Transfer Vector and Production of the Transfer Vector of the Present Invention

Production of Immunogenic Foreign Gene DNA

30 The immunogenic foreign gene DNA capable of being fused to the viral gene, which is one of the components of the baculovirus transfer vector, can be easily produced or obtained by synthesis based on the nucleic acid sequence information of the polynucleotide encoding the amino acid sequence of an antigenic protein having the desired immunogenicity disclosed in this specification, or directly synthesizing the DNA
35 corresponding to the nucleic acid sequence of the coding region

of the immunogenic foreign gene, based on the nucleic acid sequence information of the immunogenic foreign gene (chemical DNA synthesis method). General gene engineering techniques can be used for this production (see, for example, "Molecular Cloning" 5 2d Ed, Cold Spring Harbor Lab. Press (1989); Zoku Seikagaku Jikken Kouza, "Idenshi Kenkyuho I, II, III", edited by the Japanese Biochemistry Society, 1986).

Examples of methods for synthesizing the DNA include chemical synthesis means, such as the phosphate triester method 10 and the phosphate amidite method (J. Am. Chem. Soc., 89, 4801 (1967); *ibid.*, 91, 3350 (1969); Science, 150, 178 (1968); Tetrahedron Lett., 22, 1859 (1981); *ibid.*, 24, 245 (1983)) and combination methods thereof. The DNA can also be chemically synthesized by the phosphoramidite method or the triester method, 15 or synthesized by using a commercially available automatic oligonucleotide synthesizer. A double strand fragment can be obtained by synthesizing a complementary strand and annealing the complementary strand with a chemically synthesized single strand under appropriate conditions, or adding the complementary strand 20 with appropriate primer sequences to a chemically synthesized single strand using a DNA polymerase.

Specific examples of the immunogenic foreign gene DNA produced in the present invention include DNA comprising a DNA sequence encoding the amino acid sequence of a malaria antigen 25 protein, and a DNA sequence encoding the amino acid sequence of an influenza virus antigen protein.

The DNA used in the present invention is not limited to a full-length DNA sequence encoding the amino acid sequence of the polypeptide of an antigenic protein having the immunogenicity, 30 and may be a DNA sequence encoding a partial sequence thereof, as long as the protein of the amino acid sequence encoded by the DNA sequence has the immunogenicity.

The DNA of the immunogenic foreign gene used in the present invention is not limited to DNA molecules having such a 35 specific DNA sequence, and may be DNA molecules having a DNA

sequence produced by suitably selecting codons for each amino acid residue. The choice of codons can be made in accordance with a standard method, for example, by considering the frequency of codon use in the host used (Nucleic Acids Res., 9, 43(1981)).

5 The DNA of the immunogenic foreign gene used in the present invention can be produced by gene engineering techniques, more specifically by preparing a cDNA library from an appropriate origin that expresses the DNA of an immunogenic foreign gene in accordance with a standard method, and selecting a desired clone
10 from the library using an appropriate probe or antibody against the expressed product, which is specific to the immunogenic foreign gene (see, for example, Proc. Natl. Acad. Sci., USA., 78, 6613 (1981); Science, 222, 778 (1983)).

 Examples of the genomic DNA origin include various
15 cells, tissues, and cultured cells derived therefrom, which express the DNA of the immunogenic foreign gene. Extracts of erythrocytes infected with malaria parasites, and extracts of cells infected with influenza viruses are particularly preferable. The extraction and separation of total DNA and RNA from the
20 origin, separation and purification of mRNA, and the production and cloning of cDNA can be performed in accordance with standard methods.

 As described above, the DNA of the immunogenic foreign gene can be produced by using the cDNA library of each immunogen
25 prepared by extraction, separation and purification of the mRNA of the immunogenic tissue or cells from the above-mentioned extract. The DNA of the immunogenic foreign gene can also be produced by using a phage library prepared by extracting the mRNA of each immunogen, adding poly A to the RNA, collecting the poly
30 A-added RNA, producing cDNA using a reverse transcriptase, adding restriction enzyme sites to both ends of the cDNA, and incorporating the cDNA into a phage.

 The method of screening the immunogenic foreign gene DNA from the cDNA library is not particularly limited, and can be
35 performed in accordance with a usual method. Specific examples of

such methods include a method of selecting a corresponding cDNA clone by immunological screening using a specific antibody (e.g., anti-malaria antibody, anti-influenza virus antibody, etc.) against the protein produced by the cDNA; a plaque hybridization method using a probe selectively binding to the target DNA sequence; a colony hybridization method; and combinations thereof.

The probe used in such hybridization methods is usually a DNA fragment chemically synthesized based on the information on the DNA sequence of the immunogenic foreign gene. The DNA sequences of the immunogenic foreign gene already obtained or fragments thereof can also be advantageously used as the probe. A sense primer and an antisense primer designed based on the DNA sequence information of the immunogenic foreign gene can also be used as the probe for the screening.

The DNA (nucleotides) used as the probe is a partial DNA (nucleotides) corresponding to the DNA sequence of an immunogenic foreign gene. The DNA (nucleotides) has an at least 15 consecutive DNA, preferably at least 20 consecutive DNA, and more preferably at least 30 consecutive DNA sequence. A positive clone itself for producing the DNA as mentioned above can also be used as the probe.

To obtain the DNA of the immunogenic foreign gene, a DNA/RNA amplification method by PCR (Science, 230, 1350 (1985)) is preferably used. In particular, when a full length cDNA is hardly obtained from the library, the RACE method (Rapid amplification of cDNA ends; Jikken Igaku 12(6), 35(1994)), particularly the 5'-RACE method (M. A. Frohman, et al., Proc. Natl. Acad. Sci., USA., 8, 8998(1988)) is preferably used.

The primers used for PCR can be designed, based on the DNA sequence information of the immunogenic foreign gene, and synthesized in accordance with standard methods. As the primers, DNA portions (SP6 promoter/primer and T7 terminator/primer) added to both ends of a vector plasmid having the DNA of the immunogenic foreign gene incorporated therein can also be used, as described in the Examples below.

The isolation/purification of the DNA/RNA fragment amplified by PCR can be performed in accordance with standard methods, for example, by gel electrophoresis.

5 The DNA sequence of the DNA of the immunogenic foreign gene thus obtained or various DNA fragments thereof can be determined in accordance with standard methods, for example, by the dideoxy method (Proc. Natl. Acad. Sci., USA., 74, 5463(1977)) or Maxam-Gilbert method (Methods in Enzymology, 65, 499(1980)), or by simply using a commercially available sequencing kit.

10 The gene encoding the amino acids of a protein capable of being a component of viral particles may be any gene that can encode a protein that is formed into a fusion protein with an immunogenic foreign gene as mentioned above in target cells and can be expressed as a protein capable of being a component of
15 viral particles in insect cells.

Examples of the gene encoding the amino acids of a protein capable of being a component of viral particles include genes of gp64 protein (GenBank Accession No. L22858), vesicular stomatitis virus glycoprotein G (VSVG: GenBank Accession No.
20 J02428), herpes simplex virus glycoprotein (KOS: GenBank Accession No. K01760), human immunodeficiency virus type I gp120 (GenBank Accession No. U47783), human respiratory syncytial virus membrane glycoprotein (GenBank Accession No. M86651), influenza A virus hemagglutinin protein (GenBank Accession No. U38242), and
25 genes of envelope proteins of viruses closely related to baculovirus. In the present invention, the gp64 gene described in Examples below can be preferably used.

The DNA of the gene encoding the amino acids of a protein capable of being a component of viral particles can be
30 easily produced or obtained by synthesis based on the nucleic acid sequence information of the polynucleotide encoding the amino acid sequence of the polypeptide of the gene encoding the amino acids of the target protein capable of being a component of viral particles; or by directly synthesizing the DNA
35 corresponding to the nucleotide sequence encoding the amino acid

sequence, based on the amino acid sequence information of the gene encoding the amino acids of the protein capable of being a component of viral particles (chemical DNA synthesis), as in the case of the production of the DNA of the immunogenic foreign gene.

5 The DNA sequence corresponding to the nucleic acid sequence encoding the amino acids of a protein capable of being a component of viral particles is not limited to a full-length coding region, and may be DNA containing a partial DNA sequence thereof.

10 As in the case of the production of the DNA molecule of the immunogenic foreign gene, the DNA of the gene encoding the amino acids of a protein capable of being a component of viral particles can be produced by general gene engineering techniques (see, for example, Molecular Cloning 2d Ed, Cold Spring Harbor
15 Lab. Press (1989); Zoku Seikagaku Jikken Kouza, "Idenshi Kenkyuho I, II, III", edited by the Japanese Biochemistry Society, 1986).

 In the present invention, commercially available vector plasmids into which a part of the promoter that controls the expression of the immunogenic foreign gene described later
20 has been incorporated and a (partial) gene encoding the amino acids of a protein capable of being a component of viral particles has been introduced can also be used.

Vertebrate Promoters

 Examples of the vertebrate promoter (promoter capable
25 of functioning in vertebrate cells) that is one of the components of the transfer vector used in the present invention include mammalian promoters and avian promoters.

Mammalian Promoters

 Examples of the mammalian promoter (promoter capable
30 of functioning in mammalian cells) that is one of the components of the transfer vector used in the present invention include cytomegalovirus promoters, SV40 promoters, retrovirus promoters, metallothionein promoters, heat shock protein promoters, CAG promoters, elongation factor 1 α promoters, actin promoters,
35 ubiquitin promoters, albumin promoters, and MHC promoters.

Avian Promoters

Examples of the avian promoter include β actin promoters, heat shock protein promoters, elongation factor promoters, ubiquitin promoters, and albumin promoters.

5 Baculovirus Promoters

Examples of the baculovirus promoter that is one of the components of the baculovirus transfer vector used in the present invention include polyhedrin promoter, p10 promoter, iel promoter, p35 promoter, vp39 promoter, and gp64 promoter.

10 Production of Recombinant Transfer Vector

The present invention relates to a novel transfer vector having a structure capable of expressing the desired immunogenic foreign gene as an antigenic protein in both insect cells and vertebrate cells, particularly mammalian cells. The novel transfer vector produced in the present invention has a structure in which a DNA sequence encoding the amino acid sequence of the desired immunogenic protein and a DNA sequence encoding the amino acid sequence of a protein capable of being a component of viral particles are linked downstream of linked promoters comprising one vertebrate promoter, particularly a mammalian promoter, and one baculovirus promoter. The DNA regions containing the DNA sequences of the two promoters, i.e., one vertebrate promoter, particularly a mammalian promoter, and one baculovirus promoter, may be directly linked to each other, or an intervening DNA sequence may be present between the DNA sequences of the two promoters (provided, however, that the two promoters should have promoter activity in insect cells and in vertebrate cells, and particularly mammalian cells). The promoter region has a structure such that either of a vertebrate promoter, particularly a mammalian promoter, and a baculovirus promoter, linked to each other, may be disposed more closely to the gene to be expressed. In the Examples described later, a baculovirus promoter is disposed more closely to the gene to be expressed than a mammalian promoter.

35 In the above structure, the DNA sequence of the fusion

gene of a gene encoding a protein capable of being a component of viral particles and a desired immunogenic foreign gene may be such that these two genes are directly linked to each other, or an intervening DNA sequence is present between the genes

5 (provided, however, that it is necessary not to cause a frameshift of the downstream gene and the upstream gene). Preferably, the antigen-presenting domain of the protein of a foreign gene having the desired immunogenicity is fused to a protein capable of being a component of viral particles.

10 Therefore, the protein of a foreign gene having the desired immunogenicity should not be cut off from the protein capable of being a component of viral particles, but should be used in a form fused therewith.

A fusion gene containing these two genes may be

15 prepared in advance, and then incorporated into the vector. Alternatively, one of the genes may first be incorporated into the vector and then the other may be incorporated into the vector to form a fusion gene in the vector.

To produce such a transfer vector, commercially

20 available expression vectors already having some essential components of the transfer vector of the present invention, i.e., a promoter region containing a vertebrate promoter, particularly a mammalian promoter, and a baculovirus promoter, and a gene region encoding the amino acid sequence of a protein capable of

25 being a component of viral particles, may be used, and the required components can be inserted by optionally cleaving such a commercially available expression vector with restriction enzymes and incorporating other promoter to insert a fused DNA sequence of a foreign gene having the desired immunogenicity and a gene

30 encoding the amino acid sequence of a protein capable of being a component of viral particles into the cloning region of the vector, or by inserting a foreign gene having the desired immunogenicity into the N terminus side of the DNA region of a gene encoding the amino acid sequence of a protein capable of

35 being a component of viral particles, already incorporated in a

plasmid.

In the present invention, the plasmid vector having a structure capable of expressing a foreign protein having the desired immunogenicity as an antigenic protein in both insect
5 cells and vertebrate cells, particularly mammalian cells, may be produced by using a commercially available plasmid already having a partial structure thereof. The amino acid sequence of a peptide for cleaving the fusion protein with enzymes in vertebrate cells may intervene. In the transfer vector of the present invention,
10 an enhancer for increasing the transcription activity in vertebrate cells, particularly mammalian cells, may be disposed upstream of the two promoters, or a DNA sequence encoding the amino acid sequence of a signal peptide for facilitating extracellular secretion of the expressed protein from host cells
15 may be bound to the gene to be fused and expressed. To terminate the transcription, a vertebrate terminator region, such as a rabbit β globin terminator, which is effective in vertebrate cells, may be disposed downstream of the gene to be fused and expressed.

20 A transfer vector capable of expressing a fusion gene of an immunogenic foreign gene capable of expressing the desired immunogenicity in baculovirus particles and a gene encoding the amino acid sequence of a protein capable of being a component of viral particles can be thereby produced.

25 Specific examples of the transfer vector and the method for production thereof according to the present invention are as shown in the Examples described later. More specifically, transfer vectors having a structure in which a CAG promoter modified from a cytomegalovirus (CMV) promoter as a vertebrate
30 promoter, particularly a mammalian promoter, and a polyhedrin (polh) promoter, vp39 promoter, or gp64 promoter as a baculovirus promoter, are linked to each other, and a fused DNA sequence of an influenza virus antigen gene or malaria antigen gene as a foreign gene and a gp64 antigen gene as a gene encoding the amino
35 acid sequence of a protein capable of being a component of the

viral particle is inserted can be mentioned as examples of pCAP-PfCSP, pCAP-PfCSP/272, pCAP-PfCSP/467, pCAP-PfCSP(A361E), pCAP-PfCSP(A361E)/272, pCAP-PfCSP(A361E)/467, pCAP-PfCSP-76, pCAP-PfCSP-76/467, pCAP-PfCSP+209, pCAP-PfCSP+209/467, pCAP-PfCSP+76/209, pCAP-PfCSP+76/209/467, pCAP-HA1/Anhui, pCAP-HA1/Anhui/272, pCAP-HA1/Anhui/467, pCAP-HA1/Vietnam, pCAP-HA1/Vietnam/51, pCAP-HA1/Vietnam/101, pCAP-HA1/Vietnam/154, pCAP-HA1/Vietnam/201, pCAP-HA1/Vietnam/272, pCAP-HA1/Vietnam/467, pCAP-AH/345, pCAP-AH/345/467, pCAP-AH/410, pCAP-AH/410/467, pCAP-AH/473, pCAP-AH/473/467, pCAP-AH/520, pCAP-AH/520/467, pCAP-VN/346, pCAP-VN/346/467, pCAP-VN/410, pCAP-VN/410/467, pCAP-VN/473, pCAP-VN/473/467, pCAP-VN/520, pCAP-VN/520/467, pCAP-CO/full, pCAP-CO/full/467, pCAP-CO/19, pCAP-CO/19/467, pCAP-CO/76, pCAP-CO/76/467, pCAP-CO/205, pCAP-CO/205/467, pCA39-HA1/Anhui, pCA64-HA1/Anhui, pCA39-PfCSP(A361E), pCA64-PfCSP(A361E), pCAP-CO/full/VSV, pCAP-CO/19/VSV, pCAP-CO/76/VSV, pCAP-CO/205/VSV, pDual-Pfs25-PfCSP-gp64, and pDual-PfMSP1-PfCSP-gp64.

(2) Production of Recombinant Baculovirus

The present invention provides a method of producing a recombinant baculovirus comprising the step of producing a transfer vector having a structure in which a fusion gene containing at least one gene encoding a protein capable of being a component of the viral particle and at least one immunogenic foreign gene is incorporated downstream of a dual promoter consisting of two linked promoters, i.e., one vertebrate promoter and one baculovirus promoter, and the step of co-transfecting the transfer vector and a baculovirus DNA into a host cell and isolating the recombinant baculovirus.

In the above process of producing the recombinant baculovirus, the method of introducing the desired recombinant DNA (transfer vector) into the host cell and the method of transformation thereby are not particularly limited. Various methods that are well known and commonly used in this field can be used. For example, general genetic recombination techniques (e.g., Science, 224, 1431 (1984); Biochem. Biophys. Res. Comm.,

130, 692 (1985); Proc. Natl. Acad. Sci. USA, 80, 5990 (1983) can be used to prepare the recombinant baculovirus. The recombinant DNA (transfer vector) can be expressed and produced with reference to Ohno et al., "Tanpaku Jikken Protocol 1 Functional Analysis, Saibo Kogaku Bessatsu, Jikken Protocol Series, 1997, Shujun-sha". The general methods used for the handling of insect cells, gene recombination, and co-transfection may be the same as well-known methods of producing a recombinant virus in insect cells (BACULOVIRUS EXPRESSION VECTORS: A LABORATORY MANUAL, Oxford University Press, 1994).

The resulting recombinant baculovirus can be cultured in accordance with standard methods. A fusion product (expressed product) of the DNA of a foreign gene having the desired immunogenicity with the DNA encoding the amino acid sequence of a protein capable of being a component of viral particles of the present invention is expressed and produced (accumulated and secreted) inside, outside, or on the cell membrane of insect cells by the culturing of the baculovirus.

As a medium used for the culturing, various commonly used media can be selectively used according to the host cell used. The culture can be performed under conditions suitable for the growth of the host cell.

More specifically, the method of producing the recombinant baculovirus comprises the step of preparing a baculovirus DNA to be subjected to homologous recombination with a transfer vector produced above, and the step of co-transfecting the transfer vector and the baculovirus DNA into insect cells, such as Sf9 cells and Sf21 cells derived from *Spodoptera frugiperda*, and Tn5 cells (High Five cells) derived from *Trichoplusia ni*, as host cells.

The baculovirus DNA thus produced to be subjected to homologous recombination with the transfer vector may be a wild type, mutant, or recombinant baculovirus DNA. The baculovirus DNA can enhance the probability of its homologous recombination with the transfer vector of the present invention as long as it has a

DNA structure homologous to the baculovirus-derived DNA containing DNA of the dual promoter region, and DNA of a fusion gene obtained by fusion of an immunogenic foreign gene and a gene encoding a protein capable of being a component of viral
5 particles.

To induce homologous recombination, the mixing ratio of the transfer vector to the baculovirus DNA by weight is preferably about 1:1 to about 10:1.

After the co-transfection step of simultaneous
10 introduction into insect cells, the cells are cultured, and viral plaques are obtained from the culture supernatant and then suspended in a medium. The virus is eluted from agar by vortex and centrifuged to yield a solution containing the recombinant virus.

15 In the above process, commercially available products may be used as the baculovirus DNA. For example, BacVector-1000 DNA and BacVector-2000 DNA (supplied from Novagen) in which the polyhedrin gene has been removed from AcNPV can be used.

The co-transfection for the homologous recombination
20 of the obtained transfer vector and baculovirus DNA into insect cells can be performed using a commercially available vector transfection kit (BacVector Transfection Kits, supplied from Novagen) as described above in accordance with the instructions packaged with the vector transfection kit. Thus, the obtained
25 transfer vector can be co-transfected together with the baculovirus DNA into insect cells such as Sf9 cell to yield a recombinant baculovirus.

In the present invention, in accordance with the above method of producing a recombinant baculovirus, a transfer vector
30 that is any one of pCAP-PfCSP, pCAP-PfCSP/272, pCAP-PfCSP/467, pCAP-PfCSP(A361E), pCAP-PfCSP(A361E)/272, pCAP-PfCSP(A361E)/467, pCAP-PfCSP-76, pCAP-PfCSP-76/467, pCAP-PfCSP+209, pCAP-PfCSP+209/467, pCAP-PfCSP+76/209, pCAP-PfCSP+76/209/467, pCAP-HA1/Anhui, pCAP-HA1/Anhui/272, pCAP-HA1/Anhui/467, pCAP-
35 HA1/Vietnam, pCAP-HA1/Vietnam/51, pCAP-HA1/Vietnam/101, pCAP-

HA1/Vietnam/154, pCAP-HA1/Vietnam/201, pCAP-HA1/Vietnam/272, pCAP-HA1/Vietnam/467, pCAP-AH/345, pCAP-AH/345/467, pCAP-AH/410, pCAP-AH/410/467, pCAP-AH/473, pCAP-AH/473/467, pCAP-AH/520, pCAP-AH/520/467, pCAP-VN/346, pCAP-VN/346/467, pCAP-VN/410, pCAP-VN/410/467, pCAP-VN/473, pCAP-VN/473/467, pCAP-VN/520, pCAP-VN/520/467, pCAP-CO/full, pCAP-CO/full/467, pCAP-CO/19, pCAP-CO/19/467, pCAP-CO/76, pCAP-CO/76/467, pCAP-CO/205, pCAP-CO/205/467, pCA39-HA1/Anhui, pCA64-HA1/Anhui, pCA39-PfCSP(A361E), pCA64-PfCSP(A361E), pCAP-CO/full/VSV, pCAP-CO/19/VSV, pCAP-CO/76/VSV, pCAP-CO/205/VSV, pDual-Pfs25-PfCSP-gp64, and pDual-PfMSP1-PfCSP-gp64, and a baculovirus DNA can be co-transfected into Sf9 insect cells to yield a recombinant baculovirus of any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64.

In addition to the above method of producing a recombinant baculovirus, other methods of producing a recombinant

baculovirus include, for example, a method of using a transposon as a phagemid (bacmid) having the entire baculovirus genome incorporated therein to efficiently insert a foreign gene into *Escherichia coli*.

5 According to this method, a bacmid bearing a viral gene is extracted from bacterial cells and transfected into insect cells to thereby easily produce and collect a recombinant baculovirus.

10 The purification of the recombinant baculovirus of the present invention obtained by the above method of producing a recombinant baculovirus can be performed by using known virus purification methods.

15 For the purification of the recombinant baculovirus, for example, 0.5 to 1.0 mL of a stock virus obtained by the above method of producing a recombinant baculovirus is inoculated into insect cells (1×10^7 cells/10 cm dish), such as Sf9 cells, the culture supernatant is collected several days after the infection, and a virus pellet obtained by centrifugation is suspended in a buffer, such as PBS. The resulting suspension is subjected to a
20 sucrose gradient of 10 to 60%, and then centrifuged (25,000 rpm, 60 minutes, 4°C) to collect a virus band. The collected virus is further suspended in PBS, subsequently centrifuged (under the same conditions as above), and the resulting purified recombinant virus pellet is stored at 4°C in a buffer, such as PBS.

25 The infectivity titer of the above resulting purified recombinant virus can be measured by plaque assay (BACULOVIRUS EXPRESSION VECTORS: A LABORATORY MANUAL, Oxford University Press, 1994) using insect cells such as Sf9 cells.

30 In the recombinant viruses described in the Examples, the N terminus of the baculovirus protein gp64 is exposed outside the particle, whereas the C terminus thereof is inside the particle. Therefore, if the protein encoded by a foreign gene having the desired immunogenicity is fused to the N terminus of gp64, the entity thereof is exposed as a component of the viral
35 particle outside the viral protein particle in insect cells, and

thus the antigen is more easily presented, which is suitable for use as the vaccine formulation of the present invention.

(3) Pharmaceutical Composition of the Present Invention

(Pharmaceutical Containing the Recombinant Baculovirus of the Present Invention as an Active Ingredient)

The recombinant baculovirus of the present invention, which is an active ingredient of the pharmaceutical composition of the present invention, can be obtained by the genetic engineering techniques shown in the above (2).

The pharmaceutical composition of the present invention essentially contains as the active ingredient a recombinant baculovirus obtained by homologous recombination of a baculovirus DNA and a transfer vector constructed so that a fusion gene obtained by the fusion of an immunogenic foreign gene of the present invention to a gene encoding the amino acid sequence of a protein capable of being a component of the viral particle can be expressed in insect cells and vertebrate cells, particularly cells of mammals, including humans.

The present invention particularly provides a pharmaceutical composition comprising as an active ingredient a specific recombinant baculovirus that is any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-

CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-
5 CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64.

The recombinant baculovirus of the present invention that is any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-
10 CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-
15 HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-
20 CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-
25 CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64, used as an active ingredient of the pharmaceutical
30 composition of the present invention, has the action of enhancing infection-preventing effects against an infectious antigen and reducing the infectivity titer. Utilizing this action and activity, the recombinant baculovirus can be used for the treatment of diseases associated with infection of target cells
35 and tissues. Examples of target cells affected by such infection

include blood cells, hepatic cells, renal cells, brain cells, lung cells, epithelial cells, and muscular cells. Examples of tissues comprising such cells include the lung, liver, kidney, brain, arteries and veins, the stomach, intestines, urethra, skin,
5 and muscle.

The pharmaceutical composition enhances infection-preventing effects against infectious antigens, for example, malaria antigens such as sporozoite surface antigens (CSP and TRAP) of malaria parasites, merozoite surface membrane protein
10 MSP1, malaria S antigen secreted from erythrocytes infected with malaria, PfEMP1 protein present in the knobs of erythrocytes infected with malaria, SERA protein, TRAMP protein, AMA1 protein, and Pfs25 known as a transmission-blocking antigen; and influenza
15 antigens such as HA antigen, NA antigen, M2 antigen, and NP antigen, and reduces the infectivity titer (e.g., viral infectivity titer), thereby increasing the survival period and survival rate of mammals including humans, compared to the group not administered the pharmaceutical composition of the present invention. Therefore, the pharmaceutical composition is
20 particularly useful as a preventive or therapeutic agent for malaria and influenza virus infections.

The pharmaceutical composition of the invention has the action of enhancing infection-preventing effects against infectious antigens and reducing the infectivity titers, and is
25 therefore useful as a preventive or therapeutic agent for infectious diseases caused by pathogens such as influenza viruses and malaria, and complications thereof.

By using a gene immunogenic to non-human vertebrates as an immunogenic foreign gene of the transfer vector to obtain a
30 recombinant baculovirus used as an active ingredient of the pharmaceutical composition of the present invention, for example, a chicken influenza vaccine can be prepared, which has the action of enhancing infection-preventing effects against the infectious antigen and reducing the infectivity titer. By utilizing this
35 action and activity, the pharmaceutical composition can be used

for the treatment of diseases associated with the infection of target cells and tissues.

The pharmaceutical composition of the present invention can be prepared as a composition containing a
5 pharmaceutically effective amount of the recombinant baculovirus of the invention and a pharmaceutically acceptable carrier.

The infection-preventing effect of the recombinant baculovirus of the present invention in vertebrates, particularly mammals, including humans, or mammalian cells can be provided,
10 for example, by administering the pharmaceutical composition containing the recombinant baculovirus of the present invention and additives for pharmaceutical administration to vertebrates, particularly mammals, including humans, by the intramuscular, subcutaneous, intracutaneous, intraperitoneal, nasal, or
15 respiratory route, and then immunizing the vertebrates with the pharmaceutical composition containing the recombinant baculovirus of the present invention as an active ingredient several times. Respiratory administration of the pharmaceutical composition of the invention is particularly preferable.

20 The infection-preventing effect can be evaluated by comparing the survival rate of vertebrates, particularly mammals, including humans, that have been immunized with the pharmaceutical composition of the invention several times and then infected with a target pathogen with the survival rate of
25 those not administered with the pharmaceutical composition.

(4) Vaccine of the present invention

The recombinant baculovirus that is any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101,
35 AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-

HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345,
AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467,
AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-
CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-
5 CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-
VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-
CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-
CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205,
AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui,
10 AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-
CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-
CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-
PfCSP-gp64 used as the active ingredient of the pharmaceutical
composition of the present invention can enhance pathogen
15 infection-preventing effects as described in the Examples below,
and an expressed fusion product of the DNA sequence obtained by
fusion of a gene encoding the amino acid sequence of a protein
capable of being a component of viral particles and a foreign
gene with the desired immunogenicity of the present invention
20 capable of reducing the infectivity titer is produced as viral
particles budded from insect cells. When the pharmaceutical
composition of the invention is administered in the form of viral
particles to vertebrates, particularly mammals, including humans,
a foreign antigen protein contained as a component of viral
25 particles promotes acquired immunity (humoral immunity and
cellular immunity), and further, the antigenic protein as an
expressed product of the fusion DNA sequence seems to promote
acquired immunity (humoral immunity and cellular immunity) in
vertebrate cells, particularly cells of mammals, including humans.
30 Thus, the recombinant baculovirus of the present invention is
useful as a vaccine.

The present invention particularly provides a vaccine
containing as an active ingredient a specific recombinant
baculovirus that is any one of AcNPV-CAP-PfCSP, AcNPV-CAP-
35 PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-

CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64.

As in the pharmaceutical composition of the above (3), the vaccine enhances infection-preventing effects against infectious antigens such as malaria antigens such as sporozoite surface antigens (CSP and TRAP) of the malaria parasite, merozoite surface membrane protein MSP1, malaria S antigen secreted from erythrocytes infected with malaria, PfEMP1 protein present in the knobs of erythrocytes infected with malaria, SERA protein, TRAMP protein, and AMA1 protein; and influenza antigens such as influenza virus HA antigen, influenza virus NA antigen, influenza virus M2 antigen, and influenza virus NP antigen; the vaccine also reduces the infectivity titer (e.g., the viral infectivity titer), thereby increasing the survival period and survival rate of mammals, including humans, compared with the group not administered with the pharmaceutical composition of the present invention. Thus, the vaccine is particularly useful as a preventive or therapeutic agent for malaria and influenza virus

infection.

The vaccine of the invention enhances infection-preventing effects against infectious antigens and reduces the infectivity titer, and is therefore useful as a preventive or
5 therapeutic agent for infectious diseases caused by pathogens such as influenza viruses and malaria, and complications thereof.

By using a gene immunogenic to non-human vertebrates as an immunogenic foreign gene of the transfer vector to obtain a recombinant baculovirus used as an active ingredient of the
10 pharmaceutical composition of the present invention, for example, a chicken influenza vaccine, that can enhance infection-prevention effects against the infectious antigen and reduce the infectivity titer, can be prepared. By utilizing this activity, the vaccine can be used for the treatment of diseases associated
15 with the infection of target cells and tissues.

The recombinant baculovirus that is any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467,
20 AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345,
25 AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-
30 CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-

CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64, used as an active ingredient of the vaccine of the present invention, can enhance infection-preventing effects against an infectious antigen and reduce the infectivity titer.

5 By utilizing this activity, the recombinant baculovirus can be used for the treatment of diseases associated with the infection of target cells and tissues.

Examples of target cells affected by such infection include blood cells, hepatic cells, renal cells, brain cells, 10 lung cells, epithelial cells, and muscular cells. Examples of tissues containing such cells include lung, liver, kidney, brain, arterial and venous veins, stomach, intestine, urethra, skin, and muscle tissues.

The vaccine of the present invention can be prepared as a pharmaceutical composition of the above (3) containing a pharmaceutically effective amount of the recombinant baculovirus of the invention (any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, 20 AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, 35

AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64), and a pharmaceutically acceptable carrier.

5 The vaccine can be prepared in the form of a pharmaceutical composition by using a pharmaceutically acceptable carrier as used in the pharmaceutical composition of the above (3), according to a standard method. Examples of carriers include physiologically acceptable solutions, such as sterile saline and sterile buffered saline.

10 The vaccine (the formulation is hereinafter the same as in the pharmaceutical composition) can be prepared as a liposomal formulation containing as an active ingredient the recombinant baculovirus of the invention (any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64), and can be used in combination with an adjuvant.

35 Specific examples of the vaccine (the pharmaceutical

composition) of the present invention include liposomal formulations. The liposomal formulation may be one in which the recombinant baculovirus of the present invention is retained in a liposome containing an acidic phospholipid as a membrane
5 component, or containing a neutral phospholipid and an acidic phospholipid as membrane components.

The acidic phospholipid and neutral phospholipid used as membrane components are not particularly limited, and various lipids commonly used for liposomal formulations can be used alone
10 or in a combination of two or more.

The liposome membrane is produced in accordance with a standard method by using an acidic phospholipid alone or together with a neutral phospholipid. When an acidic phospholipid is used together with a neutral phospholipid, the proportion of the
15 acidic phospholipids in the liposome membrane components is preferably about 0.1 to about 100 mol%, more preferably 1 to 90 mol%, and even more preferably about 10 to about 50 mol%.

To prepare the liposome, for example, cholesterol or the like can be added. This can control the fluidity of
20 phospholipids and facilitates the liposome preparation. In general, the cholesterol is preferably added in an equivalent amount or less, and preferably in a 0.5-fold amount to an equivalent amount by weight, to the phospholipid.

The mixing ratio of the acidic phospholipid to the
25 active ingredient in the liposomal formulation is about 0.5 to about 100 equivalents, preferably about 1 to about 60 equivalents, and more preferably about 1.5 to about 20 equivalents.

The recombinant baculovirus of the present invention as an active ingredient is used in an amount of several mol% to
30 several tens mol%, preferably about 5 to about 10 mol%, and usually around 5 mol%, based on the total amount of the lipids.

The production, concentration, and particle diameter control of the liposomal formulation can be performed in accordance with standard methods. If desired, the various
35 additives as described above can also be incorporated into the

liposomal formulation.

To produce the liposomal formulation, the recombinant baculovirus of the invention as an active ingredient can be used in the form of being bound to a fatty acid (e.g., behenic acid, stearic acid, palmitic acid, myristic acid, and oleic acid), an alkyl group, a cholesteryl group, or the like. The liposomal formulation containing such bound components can also be produced in accordance with a standard method (see, for example, Long Circulating Liposomes: Old Drugs, New Therapeutics., M. C. Woodle, G. Storm, Eds: Springer-Verlag Berlin (1998)).

The vaccine (pharmaceutical composition) of the present invention can preferably be used as a vaccine composition. The vaccine is preferably used in combination with a pharmaceutically effective amount of an adjuvant to enhance the anti-infection (anti-malaria or anti-influenza) effects.

Any adjuvant commonly used for this type of vaccine can be used as the adjuvant. Examples of such adjuvants include Freund's complete adjuvant, muramyl dipeptide, aluminium hydroxide, BCG, IL-12, N-acetylmuramine-L-alanyl-D-isoglutamine (MDP), thymosin $\alpha 1$, and QS-21. The amount of adjuvant used can be suitably selected according to the degree of symptoms, such as softening of the skin, pain, erythema, fever, headache, and muscular pain, which might be expressed as part of the immune response in humans or animals after the administration of this type of vaccine.

The vaccine (pharmaceutical composition) of the present invention may be used in combination with other publicly known pharmaceutical products, such as immune response-promoting peptides and antibacterial agents (synthetic antibacterial agents).

The vaccine (pharmaceutical composition) may further contain other drugs and additives. Examples thereof include drugs that aid intracellular uptake of the recombinant baculovirus of the present invention, such as calcium ions. The liposome, and other drugs and additives that facilitate the transfection, such

as fluorocarbon emulsifiers, cochleates, tubules, golden particles, biodegradable microspheres, and cationic polymers, can also be used.

The amount of the active ingredient contained in the vaccine (pharmaceutical composition) (drug) of the present invention is not particularly limited and can be selected from a wide range as long as it is a pharmaceutically effective amount. The dosage of the vaccine (pharmaceutical composition) is not particularly limited, and can be appropriately selected from a wide range according to the desired therapeutic effect, the administration method (administration route), the therapeutic period, the patient's age, gender, and other conditions, etc.

When the recombinant baculovirus as an active ingredient of the vaccine (pharmaceutical composition) of the present invention is administered to a human, the recombinant baculovirus is administered in an amount corresponding to 10^2 to 10^{14} PFU, preferably 10^5 to 10^{12} PFU, and more preferably 10^6 to 10^{10} PFU per patient, calculated as the PFU of the recombinant virus.

The dosage of the recombinant baculovirus (any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-

CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64), used as an active ingredient of the vaccine (pharmaceutical composition) of the present invention, can be selected from a very wide range, in terms of the amount of expressible DNA introduced into the vaccine host or the amount of transcribed RNA. These amounts also depend on the strength of the transcription and translation promoters used in the transfer vector of the invention.

The vaccine (pharmaceutical composition) of the present invention is administered by directly injecting a recombinant baculovirus suspension prepared by suspending the recombinant baculovirus in PBS (phosphate buffered saline) or saline into a local site (e.g., into the lung tissue, liver, muscle or brain), or by nasal or respiratory inhalation, or by intravascular (e.g., intra-arterial, intravenous, and portal venous), subcutaneous, intracutaneous, or intraperitoneal administration. The vaccine of the invention is preferably administered by respiratory inhalation.

The vaccine (pharmaceutical composition) of the present invention is preferably administered more than once. More specifically, after the initial administration, additional vaccinations are preferably performed once to several times while the condition is observed. This can enhance the desired effect. After the administration of the vaccine (pharmaceutical composition), booster immunization with a pharmaceutical composition containing the recombinant baculovirus of the present invention (any one of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467,

AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101, AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, AcNPV-CA39-PfCSP (A361E), AcNPV-CA64-PfCSP (A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64) can be performed. Further, use of various other drugs with the vaccine of the invention, as mentioned above, may enhance the therapeutic effect achieved by the administration of the vaccine (pharmaceutical composition).

In one embodiment of the vaccine (pharmaceutical composition) of the present invention, the recombinant baculovirus, used as one of the active ingredients of the vaccine (pharmaceutical composition) of the invention, is generally prepared by homologous recombination of a baculovirus DNA and a transfer vector into which a fusion gene obtained by fusion of a foreign gene having the desired immunogenicity and a gene encoding a protein capable of being a component of viral particles has been introduced. The recombinant baculovirus is mixed, in an injectable dosage form (a solution, suspension or emulsion), with a pharmaceutically acceptable carrier (i.e., non-toxic to humans and other vertebrates in the dosage and concentration used, and compatible with other ingredients in the formulation) to produce a formulation. Preferably, the formulation thus obtained does not contain oxidizing agents or

any other compound that is publicly known to be harmful to recombinant baculovirus.

The carrier may contain a trace amount of additives, such as substances that enhance the isotonicity and chemical stability. Such additives are non-toxic to mammals, including humans, in the dosage and concentration used, and examples thereof include buffers such as phosphoric acid, citric acid, succinic acid, acetic acid, and other organic acids, and salts thereof; antioxidants such as ascorbic acid; low molecular weight (e.g., less than about 10 residues) polypeptides (e.g., polyarginine and tripeptide) proteins (e.g., serum albumin, gelatin, and immunoglobulin); amino acids (e.g., glycine, glutamic acid, aspartic acid, and arginine); monosaccharides, disaccharides, and other carbohydrates (e.g., cellulose and derivatives thereof, glucose, mannose, and dextrin), chelating agents (e.g., EDTA); sugar alcohols (e.g., mannitol and sorbitol); counterions (e.g., sodium); nonionic surfactants (e.g., polysorbate and poloxamer); and PEG.

The pharmaceutical vaccine (composition) containing the recombinant baculovirus can typically be stored as an aqueous solution or a lyophilized product in a unit or multiple dose container such as a sealed ampoule or a vial.

The present invention further provides a method of preventing malaria or influenza infection, or a method of treating malaria or influenza, comprising administering an effective amount of the recombinant baculovirus, vaccine, formulation, and pharmaceutical composition of the invention to a subject. The present invention further provides a method of immunostimulation comprising administering an effective amount of the recombinant baculovirus, vaccine, formulation, and pharmaceutical composition of the invention to a subject. Examples of the subjects used include those that may be infected with malaria parasites or influenza viruses, such as humans and other animals (such as mammals, birds, reptiles, fish, and amphibians), and those infected with malaria parasites or

influenza viruses. The influenza virus with which the subject is infected is preferably an influenza A virus, and more preferably an influenza A subtype H1 virus, or an influenza A subtype H3 virus. Examples of malaria parasites include *Plasmodium*
5 *falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*.

The recombinant baculovirus of the present invention is formed alone or together with a pharmaceutically acceptable carrier into a vaccine, formulation, or pharmaceutical
10 composition, and administered to the subject.

The administration route may be, for example, any administration route mentioned above. The pharmaceutically acceptable carrier for use in the present invention can be suitably selected from carriers commonly used in this technical
15 field, according to the form of the pharmaceutical composition to be produced.

For example, when the pharmacological composition is formed into an aqueous solution, purified water (sterile water) or a physiological buffer solution can be used as the carrier.
20 When the pharmaceutical composition is formed into other appropriate solutions, organic esters capable of being injected, such as glycol, glycerol and olive oil, can be used as the carrier. The composition may contain stabilizers, excipients and the like commonly used in this technical field, and particularly
25 in the field of vaccine formulations.

The amount of recombinant baculovirus in the vaccine, formulation, or pharmaceutical composition of the present invention is not particularly limited, and can be suitably selected from a wide range. In general, the amount of recombinant
30 baculovirus in the composition is preferably about 0.0002 to about 0.2 (w/v %), and more preferably 0.001 to 0.1 (w/v %). The administration method of the recombinant baculovirus, vaccine, formulation, or pharmaceutical composition of the invention is not particularly limited, and can be suitably selected according
35 to the dosage form, the patient's age, gender and other

conditions, the severity of the disease, etc. A preferable dosage form thereof is a form for parenteral administration, such as injections, drops, nasal drops, and inhalants. When the composition is formed into an injection or drops, the injection
5 can be intravenously administered as mixed with a replacement fluid such as a glucose solution or an amino acid solution as required, or can be administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally.

The daily dosage of the recombinant baculovirus, vaccine, formulation, or pharmaceutical composition of the
10 present invention may vary depending on the subject's condition, body weight, age, gender, etc., and therefore cannot be completely specified. However, the dosage is usually such that the recombinant baculovirus is administered in an amount of 0.001
15 to 100 mg per kg of body weight per day. The vaccine, formulation, or composition of the invention can be administered in one or more administrations per day.

When the recombinant baculovirus as an active ingredient of the vaccine (formulation or pharmaceutical
20 composition) of the present invention is administered, the recombinant baculovirus is administered in an amount corresponding to 10^2 to 10^{14} PFU, preferably 10^5 to 10^{12} PFU, and more preferably 10^6 to 10^{10} PFU per patient, calculated as the PFU of the recombinant virus.

25 The vaccine (composition) of the present invention is administered according to Good Medical Practice, considering the clinical condition (for example, the condition to be prevented or treated) of each patient, the delivery site of the vaccine (composition) containing the recombinant baculovirus, the target
30 tissue, the administration method, the dosage regimen, and other factors publicly known to those skilled in the art. Therefore, the proper dosage of the vaccine (composition) herein is determined in consideration of the above.

The present invention will be described below in more detail with reference to Examples. These Examples are merely examples of the present invention, and do not limit the present invention.

5 Example 1: Transfer Vector Plasmid and Method for Production thereof of the Present Invention

(1) Construction of Transfer Vector Plasmids pCAP-PfCSP, pCAP-PfCSP/272, and pCAP-PfCSP/467 of the Present Invention

(1.1) Construction of Plasmid pBACsurf-Hsp65

10 An Hsp65 gene was obtained by extracting genomic DNA from *M. tuberculosis* H37Rv strain using a QIAamp DNA Midi Kit (Qiagen), and cloning by PCR. More specifically, the genomic DNA extracted from the *M. tuberculosis* H37Rv strain was amplified by PCR using primers phsp65-F1 (5' -
15 AATAATAGATCTAATGGCCAAGACAATTGCGTACGACGAAGA -3' (SEQ ID NO: 1); the BglIII site is underlined) and phsp65-R1 (5' -
AATCCAATGCGGCCGCGGAATTTCGATTCCTGCAGGTCAGAAATCCATGCCACCCATGTCGCC -
3' (SEQ ID NO: 2); the NotI site is underlined). The PCR product
20 was purified, cleaved with restriction enzymes BglIII and NotI, ligated to pcDNA3.1(+) (from Invitrogen) digested with BamHI and NotI. The resulting plasmid was designated pcDNA-hsp65. PCR was performed with pcDNA-hsp65 as a template using primers phsp65-F2
(5' - CACCCCTGCAGGACTACAAGGACGACGATGACAAGGAATTCATGGCCAAGAC
AATTGCGTACGACGAAGAGGCC - 3' (SEQ ID NO: 3); the Sse8387I and
25 EcoRI sites are underlined, and the FLAG sequence is italicized), and
phsp65-R2 (5' - CCCGGGCGAAATCCATGCCACCCATGTCGCCGCCACC - 3' (SEQ
ID NO: 4); the Cfr9I site is underlined). The resulting Hsp65
gene DNA fragment was cloned into pENTR/D-TOPO (from Invitrogen),
30 then cleaved with Sse8387I/Cfr9I and inserted into the PstI/Cfr9I
site of pBACsurf-CSP (Yoshida et al., Virology 316: 161-70, 2003).
The plasmid thus constructed was designed pBACsurf-Hsp65.

(1.2) Construction of Plasmid pENTR-gp64

PCR was performed with pBACsurf-1 (from Novagen) as a
35 template using primers pPolh-F2 (5' -

CACCCGGACCGGATAATTAAATGATAACCATCTCGCAATAAATAAG - 3' (SEQ ID NO: 5); the RsrII site is underlined), and pgp64-R2 (5' - GGTACCATATTGTCTATTACGGTTTCTAATCATAC - 3' (SEQ ID NO: 6); the KpnI site is underlined). The resulting gp64 gene DNA fragment was inserted into pENTR/D-TOPO to construct a plasmid pENTR-gp64. The plasmid thus constructed was designated pENTR-gp64.

(1.3) Construction of Transfer Vector pDual-Hsp65-gp64 of the Present Invention

pBACsurf-Hsp65 was cleaved with PstI/Cfr9I, and the hsp65 gene DNA fragment was inserted into the PstI/Cfr9I site of pENTR-gp64 to construct a plasmid pENTR-Hsp65-gp64. The pENTR-Hsp65-gp64 was cleaved with RsrII/KpnI, and a DNA fragment consisting of a polyhedrin promoter and hsp65-gp64 gene was inserted into pTriEx-3.1 (Novagen) cleaved with RsrII and KpnI to construct a transfer vector plasmid pDual-Hsp65-gp64 enabling the expression of a fusion protein of Hsp65 antigen and gp64 protein in mammalian and insect cells under the control of the desired dual promoter consisting of CMA promoter and polyhedrin promoter.

(1.4) Construction of Transfer Vector pDual-H1N1/HA1-gp64 of the Present Invention

RNA was extracted from a culture supernatant of MDCK cells infected with influenza virus PR/8/34 strain using a QIAamp MinElute Virus Spin Kit (from Qiagen), and amplified by RT-PCR using primers HA-f (5' - CCTGCAGGTATGAAGGCAAACCTACTGGTC - 3' (SEQ ID NO: 7); the SbfI site is underlined) and HA-r (5' - GCCCCGGGCGATGCATATTCTGCA - 3' (SEQ ID NO: 8); the SbfI site is underlined). The resulting influenza virus HA gene fragment was cloned into PCR-Blunt II-TOPO (from Invitrogen). The resulting plasmid was designated as PCR-Blunt-HA. PCR was performed with the PCR-Blunt-HA as a template using primers pHA-F1 (5' - CACCGAATTCGACACAATATGTATAGGCTACCATGCG-3' (SEQ ID NO: 9); the EcoRI site is underlined) and pHA-R1 (5' - CCCGGGCACCTCTGGATTGGATGGACGGAATG - 3' (SEQ ID NO: 10); the Cfr9I site is underlined). The resulting H1N1/HA1 gene DNA fragment was cloned into pENTR/D-TOPO, then cleaved with EcoRI/Cfr9I and

inserted into the EcoRI/Cfr9I site of pDual-Hsp65-gp64 to construct a plasmid pDual-H1N1/HA1-gp64.

(1.5) Construction of Plasmid pBACsurf-HA1

pDual-H1N1/HA1-gp64 was cleaved with EcoRI/CfrI, and the DNA fragment of H1N1/HA1 gene was inserted into pBACsurf-Hsp65 digested with EcoRI and CfrI to construct a plasmid pBACsurf-HA1.

(1.6) Construction of Plasmid pCP-H1N1/HA1-gp64

PCR was performed with pBACsurf-HA1 as a template using Polh-f RsrII (5' - GGGCGGACCGGATAATTAAAATGATAACCATCTCG - 3' (SEQ ID NO: 11); the RsrII site is underlined) and GP64-r DraIII (5' - GGGCACTTAGTGATATTGTCTATTACGGTTTCTAATC - 3' (SEQ ID NO: 12); the DraIII site is underlined). The resulting DNA fragment was inserted into pDual-H1N1/HA1-gp64 digested with RsrII and DraIII to yield pCP-H1N1/HA1-gp64.

(1.7) Construction of Plasmid pCAP-H1N1/HA1-gp64

pCP-H1N1/HA1-gp64 was cleaved with restriction enzymes RsrII and DraIII to prepare HA1 and gp64 gene fragments. The fragments were inserted into a vector prepared by digesting pTriEx-1.1 (from Novagen) with restriction enzymes RsrII and DraIII to yield a transfer vector plasmid pCAP-H1N1/HA1-gp64 enabling the expression of a fusion protein of HA1 antigen and gp64 protein in mammalian and insect cells under the control of the desired dual promoter consisting of CAG promoter and polyhedrin promoter.

(1.8) Construction of Plasmid pCAP-H1N1/NP-gp64

RT-PCR was performed with genomic RNA of influenza virus PR/8/34 strain as a template using NP-f EcoRI (5' - ACGGAATTCCATTCAATTCAAACTGGA - 3' (SEQ ID NO: 13); the EcoRI site is underlined) and NP-r Cfr9I (5' - GATCCCGGGCCTTGTCAATGCTGAATGGCAA - 3' (SEQ ID NO: 14); the Cfr9I site is underlined). The obtained fragments were digested with restriction enzymes EcoRI and Cfr9I, and inserted into pCAP-H1N1/HA1-gp64 digested with restriction enzymes EcoRI and Cfr9I to yield pCAP-H1N1/NP-gp64.

(1.9) Construction of Plasmids pCAP-H1N1/NP/272 and pCAP-H1N1/NP/467

PCR was performed using gp64(272)-f (5' - GACTCCCCGGGTCGAGCACCGAGTCAAGAAG - 3' (SEQ ID NO: 15); the XmaI site is underlined), gp64(467)-f (5' - GACTCCCCGGGACATCACTTCCATGGCTGAA - 3' (SEQ ID NO: 16); the XmaI site is underlined), and GP64-r DraIII (5' - GGGCACTTAGTGATATTGTCTATTACGGTTTCTAATC - 3' (SEQ ID NO: 12); the DraIII site is underlined) of pCAP-H1N1/HA1-gp64. The obtained fragments were digested with restriction enzymes XmaI and DraIII, and inserted into pCAP-H1N1/NP-gp64 digested with XmaI and DraIII to yield pCAP-H1N1/NP/272 and pCAP-H1N1/NP/467.

(1.10) Construct of Transfer Vectors pCAP-PfCSP, cCAP-PfCSP/272 and pCAP-PfCSP/467 of the Present Invention

P. falciparum genomic DNA was extracted from human erythrocytes infected with *Plasmodium falciparum* 3D7 strain using a QIAamp DNA Midi Kit (from Qiagen). A PfCSP gene was cloned by PCR with this genomic DNA as a template according to the following method. The PCR was performed using primers PfCSP-f(19) (5' - GACTCTGCAGTTATTCCAGGAATACCAAGTGCTATGGAAG - 3' (SEQ ID NO: 17); the PstI site is underlined) and PfCSP-r(373) (5' - CGATCCCCGGGCTTTTTCCATTTTACAAATTTTTTTTCAATATC - 3' (SEQ ID NO: 18); the XmaI site is underlined). The resulting DNA fragment was inserted into pCAP-H1N1/NP-gp64, pCAP-H1N1/NP/272, and pCAP-H1N1/NP/467, each digested with PstI and XmaI. The constructed plasmids were designated pCAP-PfCSP, pCAP-PfCSP/272, and pCAP-PfCSP/467.

The GenBank accession number of the amino acid sequence of the *Plasmodium falciparum* 3D7 circumsporozoite (CS) protein is XP_001351122.

(2) Construction of Transfer Vector pDual-Pfs25-PfCSP-gp64 of the Present Invention

(2.1) Construction of Plasmid pDual-PbAMA1D123-gp64

A blood sample was collected from a BALB/c mouse infected with malaria parasite *P. berghei* ANKA strain, and *P.*

berghei genomic DNA was extracted using a QIAamp DNA Midi Kit (Qiagen). A PbAMA1 gene domain 123 (D123) was cloned by PCR with this genomic DNA as a template according to the following method. PCR was performed using primers pAMA-F1 (5' -
5 CACCGAATTCAATCCATGGGAAAAGTATACGGAAAATAT - 3' (SEQ ID NO: 19); the EcoRI site is underlined) and pAMA1-R1 (5' -
CCCCGGCTTCTCTGGTTTGATGGGCTTTCATATGCAC - 3' (SEQ ID NO: 20); the Cfr9I site is underlined). The resulting PbAMA1D123 DNA fragment was cloned into pENTR/D-TOPO, then cleaved with EcoRI/Cfr9I and
10 inserted into pBACsurf-Hsp65 digested with EcoRI and Cfr9I. The constructed plasmid was designated pBACsurf-PbAMA1D123.

Subsequently, the pBACsurf-PbAMA1D123 was cleaved with EcoRI/Cfr9I, and the PbAMA1D123 gene DNA fragment was inserted into pDual-Hsp65-gp64 digested with EcoRI and Cfr9I to yield a
15 plasmid pDual-PbAMA1D123-gp64.

(2.2) Construction of Plasmid pDual-PfCSP-gp64

A PfCSP gene was cloned by PCR with *P. falciparum* genomic DNA as a template according to the following method. The PCR was performed using primers pPfCSP-F1 (5' -
20 CACCGAATTCTTATTCCAGGAATACCACTGCTATGGAAGT-3' (SEQ ID NO: 21); the EcoRI site is underlined) and pPfCSP-R1 (5' -
CCCCGGCTTTTTCATTTTACAAATTTTTTTTTTC-3' (SEQ ID NO: 22); the Cfr9I site is underlined). The resulting PfCSP DNA fragment was cloned into pENTR/D-TOPO, then cleaved with EcoRI/Cfr9I and inserted
25 into pDual-PbAMA1D123-gp64 digested with EcoRI and Cfr9I. The constructed plasmid was designated pDual-PfCSP-gp64.

(2.3) Construction of Transfer Vector pDual-Pfs25-PfCSP-gp64 of the Present Invention

A Pfs25 gene was cloned by PCR with *P. falciparum*
30 genomic DNA as a template according to the following method. The PCR was performed using primers pPfs25-F1 (5' -
CACCGAATTCAAAGTTACCGTGGATACTGTATGCAAAGAGGA - 3' (SEQ ID NO: 23); the EcoRI site is underlined) and pPfs25-R2 (5' -
CAATTGAGATCCGCCGCCACCGCCACCAGTACATATAGAGCTTTCATTATCTATTATAAATCCAT
35 C - 3' (SEQ ID NO: 24); the MunI site is underlined). The

resulting Pfs25 DNA fragment was cloned into pENTR/D-TOPO, then cleaved with EcoRI/MunI, and inserted into pDual-PfCSP-gp64 digested with EcoRI. The constructed plasmid was designated pDual-Pfs25-PfCSP-gp64.

- 5 (3) Construction of Transfer Plasmid pDual-PfMSP1-PfCSP-gp64 of the Present Invention

A PfMSP1 gene was cloned by PCR with *P. falciparum* genomic DNA as a template according to the following method. The PCR was performed using primers pPfMSP119-F1 (5' -
10 CACCGAATTCAACATTTTCACAACACCAATGCGTAAAAAAC - 3': (SEQ ID NO: 25); the EcoRI site is underlined) and pPfMSP119-R2 (5' - CAATTGAGATCCGCCGCCACCGCCACCGTTAGAGGAACTGCAGAAAATACCATCGAAAAGTGG - 3' (SEQ ID NO: 26); the MunI site is underlined). The resulting PfMSP119 DNA fragment was cloned into pENTR/D-TOPO, then cleaved
15 with EcoRI and MunI, and inserted into pDual-PbCSP-gp64 digested with EcoRI. The constructed plasmid was designated pDual-PfMSP1-PfCSP-gp64.

- (4) Construction of the Transfer Vector Plasmids pCAP-PfCSP(A361E), pCAP-PfCSP(A361E)/272, and pCAP-PfCSP(A361E)/467 of
20 the Present Invention

PCR was performed with pCAP-PfCSP using PfCSP-f(19) (5' -GACTCTGCAGTTATTCCAGGAATACCAGTGCTATGGAAG-3': (SEQ ID NO: 17); the PstI site is underlined) and PfCSP-r(373 A361E) (5' -
CGATCCCCGGGCTTTTTCCATTTTACAAATTTTTTTTTTCAATATCATTTTC-3': (SEQ ID
25 NO: 27); the XmaI site is underlined). The obtained DNA fragment was cleaved with PstI and XmaI, and inserted into pCAP-H1N1/NP-gp64, pCAP-H1N1/NP/272, and pCAP-H1N1/NP/467, each digested with PstI and XmaI. The constructed plasmids were designated pCAP-PfCSP(A361E), pCAP-PfCSP(A361E)/272, and pCAP-PfCSP(A361E)/467.

- 30 (5) Construction of Transfer Plasmids pCAP-PfCSP-76 and pCAP-PfCSP-76/467 of the Present Invention

PCR was performed with pCAP-PfCSP(A361E) using PfCSP-f(76) (5' -GACTCTGCAGGATGATGGAAATAACGAAGACAACG - 3': (SEQ ID NO: 28); the PstI site is underlined) and PfCSP-r(373 A361E) (5' -
35 CGATCCCCGGGCTTTTTCCATTTTACAAATTTTTTTTTTCAATATCATTTTC - 3': (SEQ ID

NO: 27); the XmaI site is underlined). The resulting DNA fragment was cleaved with PstI and XmaI, and then inserted into pCAP-H1N1/NP-gp64 and pCAP-H1N1/NP/467, each cleaved with PstI and XmaI. The constructed plasmids were designated pCAP-PfCSP-76 and pCAP-PfCSP-76/467.

(6) Construction of Transfer Plasmids pCAP-PfCSP+209 and pCAP-PfCSP+209/467

An artificial gene sequence (PfCSP+: SEQ ID NO: 29) was prepared from the amino acid sequence of PfCSP of *P. falciparum* 3D7 strain (in which, however, the A at the 361-position was replaced by E) using codons frequently used in Sf9 and human cells. Using the obtained artificial gene sequence as a template, PCR was performed using PfCSP-f(+209) (5'-GACTCTGCAGAACGCTAATCCAAACGCTAATCCCAACGCTAATCCCAATGCC -3' (SEQ ID NO: 30); the PstI site is underlined) and PfCSP-r(+A361E) (5'-CGATCCCGGGCTTTTTCATTTTGCAAATTTTTTTT -3' (SEQ ID NO: 31); the XmaI site is underlined). The resulting DNA fragments were cleaved with PstI and XmaII, and then inserted into pCAP-H1N1/NP-gp64 and pCAP-H1N1/NP/467 digested with PstI and XmaII. The constructed plasmids were designated pCAP-PfCSP+209 and pCAP-PfCSP+209/467.

(7) Construction of Transfer Plasmids pCAP-PfCSP+76/209 and pCAP-PfCSP+76/209/467 of the Present Invention

Using the artificial gene sequence (PfCSP+: SEQ ID NO: 29) as a template, PCR was performed using PfCSP-f(+76) (5'-GACTCTGCAGGACGACGGCAACAACGAAGACAACG -3' (SEQ ID NO: 32); the PstI site is underlined), PfCSP-r(+128) (5'-CGTTAGGATCCACATTTGGGTGGCATTTGGG -3' (SEQ ID NO: 33); the BamH I site is underlined), PfCSP-f (+209) BamHl (5'-GACTGGATCCTAACGCTAATCCAAACGCTAATCCC- 3': (SEQ ID NO: 34); the BamH I site is underlined), and PfCSP-r(+A361E) (5'-CGATCCCGGGCTTTTTCATTTTGCAAATTTTTTTT -3' (SEQ ID NO: 31); the XmaI site is underlined) from the obtained artificial gene sequence. The resulting DNA fragments were cleaved with PstI/BamHl and BamHl/XmaI, respectively, and then inserted into pCAP-H1N1/NP-gp64 and pCAP-H1N1/NP/467, each digested with PstI and XmaI. The

constructed plasmids were designated pCAP-PfCSP+76/209 and pCAP-PfCSP+76/209/467.

(8) Construction of Transfer Plasmids pCAP-HA1/Anhui, pCAP-HA1/Anhui/272, and pCAP-HA1/Anhui/467

5 An artificial gene sequence (SEQ ID NO: 35) was prepared from the amino acid sequence of the hemagglutinin HA1 region of influenza virus H5N1/Anhui/1/05 using codons frequently used in Sf9 and human cells. Using the obtained artificial gene sequence as a template, PCR was performed using AH-F1 (5'-
10 CAGTCTGCAGGACCAGATTTGCATC-3': (SEQ ID NO: 36); the PstI site is underlined) and AH-R4 (5'-CAGTCCCGGGCTCTCTTGCGCCTGC-3': (SEQ ID NO: 37); the XmaI site is underlined). The obtained DNA fragment was cleaved with PstI and XmaI, and then inserted into pCAP-H1N1/NP-gp64, pCAP-H1N1/NP/272 and pCAP-H1N1/NP/467, each
15 digested with PstI and XmaI. The constructed plasmids were designated pCAP-HA1/Anhui, pCAP-HA1/Anhui/272, and pCAP-HA1/Anhui/467.

 The GenBank accession number of the amino acid sequence of the hemagglutinin of influenza virus
20 A/H5N1/Anhui/1/05 is ABD28180.

(9) Construction of Transfer Vector Plasmids pCAP-HA1/Vietnam, pCAP-HA1/Vietnam/51, pCAP-HA1/Vietnam/101, pCAP-HA1/Vietnam/154, pCAP-HA1/Vietnam/201, pCAP-HA1/Vietnam/272, and pCAP-HA1/Vietnam/467 of the Present Invention

25 An artificial gene sequence (SEQ ID NO: 38) was prepared from the amino acid sequence of the HA1 region of the hemagglutinin of influenza virus H5N1/Vietnam/1203/4 using codons frequently used in Sf9 and human cells. Using the obtained artificial gene sequence as a template, PCR was performed using
30 VN-F1 (5'-CAGTCTGCAGGACCAGATCTGTATC-3': (SEQ ID NO: 39); the PstI site is underlined), and VN-R4 (5'-CAGTCCCGGGCTCTCTTCTTCTCCTGC-3': (SEQ ID NO: 40); the XmaI site is underlined). The obtained DNA fragment was cleaved with PstI and XmaI, and inserted into pCAP-H1N1/NP-gp64, pCAP-H1N1/NP/272 and pCAP-H1N1/NP/467, each
35 digested with PstI and XmaI. The constructed plasmids were

designated pCAP-HA1/Vietnam, pCAP-HA1/Vietnam/272, and pCAP-HA1/Vietnam/467.

Further, using pCAP-HA1/Vietnam as a template, PCR was performed using gp64(51)-f (5'-

- 5 GACTCCCCGGGTGGAAATCACCATCGTGGAGACG-3': (SEQ ID NO: 41); the XmaI site is underlined), or gp64(101)-f (5'-
GACTCCCCGGGATTGCTTATGTGGAGCATCAGG-3': (SEQ ID NO: 42); the XmaI site is underlined), or gp64(154)-f (5'-
GACTCCCCGGGCGCACCACACGTGCAACAAATCG-3': (SEQ ID NO: 43); the XmaI
10 site is underlined), or gp64(201)-f (5'-
GACTCCCCGGGACACTGTGCTTCATCGAGACGGC-3': (SEQ ID NO: 44); the XmaI site is underlined), and GP64-r DraIII (5'-
GGGCACTTAGTGATATTGTCTATTACGGTTTCTAATC-3' (SEQ ID NO: 12); the
DraIII site is underlined). The obtained DNA fragments were
15 cleaved with XmaI and DraIII, and inserted into pCAP-HA1/Vietnam digested with XmaI and DraIII. The constructed plasmids were designated pCAP-HA1/Vietnam/51, pCAP-HA1/Vietnam/101, pCAP-HA1/Vietnam/154, and pCAP-HA1/Vietnam/201.

- The GenBank accession number of the amino acid
20 sequence of the hemagglutinin of influenza virus A/H5N1/Vietnam/1203/2004 is AAW80717.

(10) Construction of Transfer Vector Plasmids pCAP-AH/345, pCAP-AH/345/467, pCAP-AH/410, pCAP-AH/410/467, pCAP-AH/473, pCAP-AH/473/467, pCAP-AH/520, pCAP-AH/520/467 of the Present Invention

- 25 An artificial gene sequence (SEQ ID NO: 45) was prepared from the amino acid sequence of the HA region of the hemagglutinin of influenza virus A/H5N1/Anhui/1/05 by codon optimization using Gene Designer available from DNA2.0, Inc. Using this artificial sequence as a template, PCR was performed
30 using AH17-F (5'-GACTCTGCAGGATCAGATCTGTATTGGGTACC-3': (SEQ ID NO: 46); the PstI site is underlined, and AH345-R (5'-
CGATCCCCGGGCTCTCTTTCTCCTCCGTCGC-3': (SEQ ID NO: 47); the XmaI site is underlined), or AH410-R (5'-
CGATCCCCGGGCGGCCTCGAACTGGGTGTTTCATT-3': (SEQ ID NO: 48); the XmaI
35 site is underlined), or AH473-R (5'-

- CGATCCCCGGGCGTCTCTGAGTTGAAGGCGCAC-3': (SEQ ID NO: 49); the XmaI site is underlined, or AH520-R (5'-
- CGATCCCCGGGCACCACTAATTCCTCTCGCTTC-3': (SEQ ID NO: 50); the XmaI site is underlined). The obtained DNA fragment was cleaved with
- 5 PstI and XmaI, and inserted into pCAP-HA1/Anhui or pCAP-HA1/Anhui/467 digested with PstI and XmaI. The constructed plasmids were designated pCAP-AH/345, pCAP-AH/345/467, pCAP-AH/410, pCAP-AH/410/467, pCAP-AH/473, pCAP-AH/473/467, pCAP-AH/520, and pCAP-AH/520/467.
- 10 (11) Construction of Transfer Vector Plasmids pCAP-VN/346, pCAP-VN/346/467, pCAP-VN/410, pCAP-VN/410/467, pCAP-VN/473, pCAP-VN/473/467, pCAP-VN/520, and pCAP-VN/520/467 of the Present Invention
- An artificial gene sequence (SEQ ID NO: 51) was
- 15 prepared from the amino acid sequence of the HA region of the hemagglutinin of influenza virus A/H5N1/Vietnam/1203/2004 by codon optimization using Gene Designer available from DNA2.0, Inc. Using this artificial sequence as a template, PCR was performed using VN17-F (5'-GACTCTGCAGGATCAGATCTGTATCGGATATC-3': (SEQ ID NO:
- 20 52); the PstI site is underlined), and VN346-R (5'-CGATCCCCGGGCCCCTTTTCCTCTCCGTTTCG-3': (SEQ ID NO: 53); the XmaI site is underlined), or VN410-R (5'-CGATCCCCGGGCCTCAAACCTGCGTATTCATTTTG-3': (SEQ ID NO: 54); the XmaI site is underlined), or VN473-R (5'-
- 25 CGATCCCCGGGGCTCTAAGCTGGAGCCTGACTTTGTC-3': (SEQ ID NO: 55); the XmaI site is underlined), or VN520-R (5'-CGATCCCCGGGCACTAATCTCCTCTCTTTTAAGTC-3': (SEQ ID NO: 56); the XmaI site is underlined). The obtained DNA fragment was cleaved with PstI and XmaI, and inserted into pCAP-HA1/Anhui or pCAP-
- 30 HA1/Anhui/467 digested with PstI and XmaI. The constructed plasmids were designated pCAP-VN/346, pCAP-VN/346/467, pCAP-VN/410, pCAP-VN/410/467, pCAP-VN/473, pCAP-VN/473/467, pCAP-VN/520, and pCAP-VN/520/467.
- (12) Construction of Transfer Vector Plasmids pCAP-CO/full, pCAP-
- 35 CO/full/467, pCAP-CO/19, pCAP-CO/19/467, pCAP-CO/76, pCAP-

CO/76/467, pCAP-CO/205, and pCAP-CO/205/467 of the Present Invention

An artificial gene sequence (SEQ ID NO: 57) was prepared from the amino acid sequence of the CSP of *Plasmodium falciparum* 3D7 strain by codon optimization using Gene Designer available from DNA2.0, Inc. Using this artificial sequence as a template, PCR was performed using a pair of primers consisting of PfcSP_opt-f (5'-GACTCTGCAGATGATGCGAAAATTGGCCATACTG-3': (SEQ ID NO: 58); the PstI site is underlined) and PfcSP_opt-r (397) (5'-CGATCCCGGGCATTGAGGAACAGAAAGGAAAGAACCATG-3': (SEQ ID NO: 59); the XmaI site is underlined); PfcSP_opt-f (19) (5'-GACTCTGCAGCTGTTTCAGGAATACCAGTGCTATGG-3': (SEQ ID NO: 60); (the PstI site is underlined) and PfcSP_opt-r (373) (5'-CGATCCCGGGCCTTCTCCATCTTACAAATTTTCTTTCAATATCATTAGC-3': (SEQ ID NO: 61); the XmaI site is underlined); PfcSP_opt-f (76) (5'-GACTCTGCAGGACGACGGAAATAATGAGGACAACG-3': (SEQ ID NO: 62); the PstI site is underlined) and PfcSP_opt-r (373) (5'-CGATCCCGGGCCTTCTCCATCTTACAAATTTTCTTTCAATATCATTAGC-3': (SEQ ID NO: 61); the XmaI site is underlined); and PfcSP_opt-f (205) (5'-GACTCTGCAGAATGCAAACCCAAATGCCAATCCAAACGC-3': (SEQ ID NO: 63); the PstI site is underlined) and PfcSP_opt-r (373) (5'-CGATCCCGGGCCTTCTCCATCTTACAAATTTTCTTTCAATATCATTAGC-3': (SEQ ID NO: 61); the XmaI site is underlined). The obtained DNA fragments were cleaved with PstI and XmaI, and inserted into pCAP-HA1/Anhui or pCAP-HA1/Anhui/467 digested with PstI and XmaI. The constructed plasmids were designated pCAP-CO/full, pCAP-CO/full/467, pCAP-CO/19, pCAP-CO/19/467, pCAP-CO/76, pCAP-CO/76/467, pCAP-CO/205, and pCAP-CO/205/467.

(13) Construction of Transfer Vector Plasmids pCA64-HA1/Anhui and pCA64-PfcSP(A361E) of the Present Invention

Using the Triple Cut DNA of BacVector-2000 DNA (from Novagen), PCR was performed using gp64-p-f (5'-GACTCGGACCGGCCAGATAAAAATAATCTTATCAATTAAG-3': (SEQ ID NO: 64); the RsrII site is underlined) and gp64-p-r (5'-CGATACTAGTAGCACTGAGGCTTCTTATATACCCG-3': (SEQ ID NO: 65); the SpeI

site is underlined). The obtained DNA fragment was cleaved with RsrII and SpeI, and inserted into pCAP-HA1/Anhui or pCAP-PfCSP(A361E) digested with RsrII and SpeI to construct transfer vector plasmids pCA64-HA1/Anhui and pCA64-PfCSP(A361E) enabling the expression of a fusion protein of HA1 antigen or PfCSP antigen and gp64 protein in mammalian and insect cells under the control of the desired dual promoter consisting of CAG promoter and gp64 promoter.

(14) Construction of Transfer Vector Plasmids pCA39-HA1/Anhui and pCA39-PfCSP(A361E) of the Present Invention

Using the Triple Cut DNA of BacVector-2000 DNA (from Novagen), PCR was performed using vp39-p-f (5'-GACTCGGACCGCGTCGTACAAATCGAAATATTGTTGTG-3': (SEQ ID NO: 66); the RsrII site is underlined) and vp39-p-r (5'-CGATACTAGTGTGATTGAGAAAGAAATCTCTTATTC-3': (SEQ ID NO: 67); the SpeI site is underlined). The obtained DNA fragment was cleaved with RsrII and SpeI, and inserted into pCAP-HA1/Anhui or pCAP-PfCSP(A361E) digested with RsrII and SpeI to construct transfer vector plasmids pCA39-HA1/Anhui and pCA39-PfCSP(A361E) enabling the expression of a fusion protein of HA1 antigen or PfCSP antigen and gp64 protein in mammalian and insect cells under the control of the desired dual promoter consisting of CAG promoter and vp39 promoter.

(15) pCAP-CO/full/VSV, pCAP-CO/19/VSV, pCAP-CO/76/VSV, and pCAP-CO/205/VSV of the Present Invention

Using pVSV-G (from Clontech) as a template, PCR was performed using VSV-G-f (5'-GACTCCCCGGGCGTTCGAACATCCTCACATTCAAG-3' (SEQ ID NO: 68); the XmaI site is underlined), VSV-G-r (5'-GACTCACTTAGTGCTTTCCAAGTCGGTTCATCTC-3': (SEQ ID NO: 69); the DraIII site is underlined). The obtained DNA fragment was inserted into pCAP-CO/full, pCAP-CO/19, pCAP-CO/76, and pCAP-CO/205, each digested with XmaI and DraIII. The constructed plasmids were designated pCAP-CO/full/VSV, pCAP-CO/19/VSV, pCAP-CO/76/VSV, and pCAP-CO/205/VSV.

Example 2: Recombinant Baculoviruses of the Present Invention and

Method for Production thereof

- (1) Recombinant baculoviruses were produced using a kit for producing recombinant baculoviruses (BacVector-2000 Transfection Kit from Novagen) by co-transfecting BacVector-2000
- 5 DNA with each of the following transfer vectors constructed in Example 1: pCAP-PfCSP, pCAP-PfCSP/272, pCAP-PfCSP/467, pCAP-PfCSP(A361E), pCAP-PfCSP(A361E)/272, pCAP-PfCSP(A361E)/467, pCAP-PfCSP-76, pCAP-PfCSP-76/467, pCAP-PfCSP+209, pCAP-PfCSP+209/467, pCAP-PfCSP+76/209, pCAP-PfCSP+76/209/467, pCAP-HA1/Anhui, pCAP-
- 10 HA1/Anhui/272, pCAP-HA1/Anhui/467, pCAP-HA1/Vietnam, pCAP-HA1/Vietnam/51, pCAP-HA1/Vietnam/101, pCAP-HA1/Vietnam/154, pCAP-HA1/Vietnam/201, pCAP-HA1/Vietnam/272, pCAP-HA1/Vietnam/467, pCAP-AH/345, pCAP-AH/345/467, pCAP-AH/410, pCAP-AH/410/467, pCAP-AH/473, pCAP-AH/473/467, pCAP-AH/520, pCAP-AH/520/467, pCAP-
- 15 VN/346, pCAP-VN/346/467, pCAP-VN/410, pCAP-VN/410/467, pCAP-VN/473, pCAP-VN/473/467, pCAP-VN/520, pCAP-VN/520/467, pCAP-CO/full, pCAP-CO/full/467, pCAP-CO/19, pCAP-CO/19/467, pCAP-CO/76, pCAP-CO/76/467, pCAP-CO/205, pCAP-CO/205/467, pCA39-HA1/Anhui, pCA64-HA1/Anhui, pCA39-PfCSP(A361E), pCA64-PfCSP(A361E), pCAP-
- 20 CO/full/VSV, pCAP-CO/19/VSV, pCAP-CO/76/VSV, pCAP-CO/205/VSV, pDual-Pfs25-PfCSP-gp64, pDual-PfMSP1-PfCSP-gp64 into Sf9 cells. The resulting recombinant baculoviruses were designated AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-PfCSP(A361E), AcNPV-CAP-PfCSP(A361E)/272, AcNPV-CAP-
- 25 PfCSP(A361E)/467, AcNPV-CAP-PfCSP-76, AcNPV-CAP-PfCSP-76/467, AcNPV-CAP-PfCSP+209, AcNPV-CAP-PfCSP+209/467, AcNPV-CAP-PfCSP+76/209, AcNPV-CAP-PfCSP+76/209/467, AcNPV-CAP-HA1/Anhui, AcNPV-CAP-HA1/Anhui/272, AcNPV-CAP-HA1/Anhui/467, AcNPV-CAP-HA1/Vietnam, AcNPV-CAP-HA1/Vietnam/51, AcNPV-CAP-HA1/Vietnam/101,
- 30 AcNPV-CAP-HA1/Vietnam/154, AcNPV-CAP-HA1/Vietnam/201, AcNPV-CAP-HA1/Vietnam/272, AcNPV-CAP-HA1/Vietnam/467, AcNPV-CAP-AH/345, AcNPV-CAP-AH/345/467, AcNPV-CAP-AH/410, AcNPV-CAP-AH/410/467, AcNPV-CAP-AH/473, AcNPV-CAP-AH/473/467, AcNPV-CAP-AH/520, AcNPV-CAP-AH/520/467, AcNPV-CAP-VN/346, AcNPV-CAP-VN/346/467, AcNPV-
- 35 CAP-VN/410, AcNPV-CAP-VN/410/467, AcNPV-CAP-VN/473, AcNPV-CAP-

VN/473/467, AcNPV-CAP-VN/520, AcNPV-CAP-VN/520/467, AcNPV-CAP-CO/full, AcNPV-CAP-CO/full/467, AcNPV-CAP-CO/19, AcNPV-CAP-CO/19/467, AcNPV-CAP-CO/76, AcNPV-CAP-CO/76/467, AcNPV-CAP-CO/205, AcNPV-CAP-CO/205/467, AcNPV-CA39-HA1/Anhui, AcNPV-CA64-HA1/Anhui, 5 AcNPV-CA39-PfCSP(A361E), AcNPV-CA64-PfCSP(A361E), AcNPV-CAP-CO/full/VSV, AcNPV-CAP-CO/19/VSV, AcNPV-CAP-CO/76/VSV, AcNPV-CAP-CO/205/VSV, AcNPV-Dual-Pfs25-PfCSP-gp64, and AcNPV-Dual-PfMSP1-PfCSP-gp64.

Example 3: Test of Expression of Vaccine Antigen from Recombinant
10 Baculovirus of the Present Invention in Insect Cells

Sf9 cells were cultured at a concentration of 1×10^5 cells per well in a 48-well plate (from Corning), and infected with baculoviruses AcNPV-CAP-PfCSP, AcNPV-CAP-HA1/Anhui, and AcNPV-CAP-HA1/Vietnam obtained in Example 2, or a wild-type
15 baculovirus AcNPV-WT as a control at an infection multiplicity of about 0.1. After 5 days, the culture supernatant was removed from each well, and then Sample Buffer Solution (+2ME, x2) (from Wako) was added in an amount of 0.05 mL per well to completely lyse the cells. The cell lysate was heated at 100°C for 5 minutes, and
20 electrophoresed on 7.5% SDS-PAGE. After electrophoresis, the protein was transferred to a PVDF membrane (Immobilon-P from Millipore), and blocking was performed at 4°C overnight by immersing the membrane in 2.5% Skim Milk/SuperBlock (from Pierce). The membrane to which the protein of Sf9 cells infected with each
25 baculovirus had been transferred was incubated with an anti-gp64 antibody (AcV5 from eBioScience) as the primary antibody, and then incubated with a HRP-labeled goat anti-mouse IgG (H+L) antibody (from BioRad) as the second antibody. Color was developed with an ECLplus Western Blotting Detection kit (from GE
30 Healthcare) to detect the protein band. FIG. 1 shows the results.

FIG. 1 shows Western blotting analysis showing the expression of fusion antigens in insect cells from recombinant baculoviruses containing PfCSP gene of human malaria, HA1 gene of influenza virus H5N1/Anhui/1/05 strain, and HA1 gene of
35 H5N1/Vietnam/1203/04 strain. In FIG. 1, Lane 1 shows the band of

a wild-type baculovirus (AcNPV-WT); Lane 2 shows the band of a recombinant baculovirus (AcNPV-CAP-PfCSP) containing PfCSP gene and full-length gp64 gene inserted downstream of the dual promoter of the present invention; Lane 3 shows the band of a recombinant baculovirus (AcNPV-CAP-HA1/Anhui) containing HA1 gene of influenza virus H5N1/Anhui/1/05 strain and full-length gp64 gene inserted downstream of the dual promoter of the present invention; and Lane 4 shows the band of a recombinant baculovirus ((AcNPV-CAP-HA1/Vietnam) containing HA1 gene of influenza virus H5N1/Vietnam/1203/04 strain and full-length gp64 gene inserted downstream of the dual promoter of the present invention.

As shown in Lanes 2, 3 and 4 of FIG. 1, a band corresponding to the expressed fusion product of an immunogenic foreign antigen gene and gp64 gene was observed in the recombinant baculoviruses having an antigen gene and gp64 gene fused and expressed downstream of the dual promoter of the present invention.

The above results confirmed that when using the recombinant virus of the present invention, an immunogenic foreign antigen gene and gp64 gene can be fused and expressed as an expressed fusion product in insect cells.

Example 4: Test of Identification of Fusion Antigen in Vaccine Antigen Presented on Viral Particle (Virion) of Recombinant Baculovirus of the Present Invention

Sf9 cells were cultured to a concentration of 1×10^7 cells per 150 mm cell culture plate (from Sumilon), and infected with each of the above-mentioned baculoviruses at an infection multiplicity of about 0.1. After 7 days, the medium was centrifuged at 3,000 xg at 4°C for 15 minutes twice, and the virus solution was layered over a 25% sucrose solution, and centrifuged using an ultracentrifuge at 25,000 rpm at 4°C for 90 minutes to yield viral particles. 0.05 mL of Sample Buffer Solution (+2ME, x2) (from Wako) was added to 0.05 mL each of the virus concentrates (1×10^8 PFU/mL) of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, AcNPV-CAP-PfCSP/467, AcNPV-CAP-HA1/Vietnam, and AcNPV-

WT collected by ultracentrifugation. The resulting mixtures were heated at 100°C for 5 minutes, and electrophoresed on 7.5% SDS-PAGE. After the electrophoresis, the obtained proteins were transferred to PVDF membranes (Immobilon-P from Millipore), and
5 immersed in 2.5% Skim Milk/SuperBlock (from Pierce) to perform blocking at 4°C overnight. The membranes to which the virus solutions of AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/272, and AcNPV-CAP-PfCSP/467 had been transferred were incubated with an anti-PfCSP antibody (2A10, MR-4) as the primary antibody, and then incubated
10 with a HRP-labeled goat anti-mouse IgG (H+L) antibody (from BioRad) as the second antibody. The membrane to which the virus solution of AcNPV-CAP-HA1/Vietnam had been transferred was incubated with an anti-H5N1 antibody (IT-003-005 from Immune Technology) as the primary antibody, and then incubated with a
15 HRP-labeled goat anti-rabbit IgG antibody (from GE Healthcare) as the second antibody. Color was developed with an ECLplus Western Blotting Detection kit (from GE Healthcare) to detect the bands of the proteins. FIG. 2 shows the results.

FIG. 2 (A) shows Western blotting analysis showing the
20 expression of the CSP gene (PfCSP) of human malaria in viral particles of recombinant baculoviruses prepared using recombinant transfer vectors. Lane 1, the left side lane of FIG. 2 (A), shows the band of a recombinant baculovirus (AcNPV-CAP-PfCSP) containing PfCSP gene and full-length gp64 gene inserted
25 downstream of the dual promoter of the invention; Lane 2 shows the band of a recombinant baculovirus (AcNPV-CAP-PfCSP/272) containing PfCSP gene and partial-length gp64 gene (241 amino acid residues from the C terminus) inserted downstream of the dual promoter of the invention; Lane 3 shows the band of a
30 recombinant baculovirus (AcNPV-CAP-PfCSP/467) containing PfCSP gene and partial-length gp64 gene (46 amino acid residues from the C terminus) inserted downstream of the dual promoter of the invention. The baculoviruses were electrophoresed, and the presence of an expressed fusion product of the PfCSP gene and
35 gp64 gene was checked. A strong band, indicating the presence of

a fusion antigen of PfcSP gene and gp64 gene in the recombinant viral particles, was detected in all the lanes of FIG. 2 (A).

FIG. 2 (B) shows Western blotting analysis showing the expression of H5N1/HA1 gene in viral particles of recombinant baculoviruses prepared using recombinant transfer vectors. Lane 1, left side lane of FIG. 2 (B), shows the results obtained using the infected AcNPV-WT cell lysate prepared in Example 3; Lane 2 shows the results obtained using the AcNPV-CAP-HA1/Anhui-infected cell lysate prepared in Example 3; Lane 3 shows the results obtained using the AcNPV-CAP-HA1/Vietnam-infected cell lysate prepared in Example 3; and Lane 4 shows the results of viral particles of a wild-type baculovirus (AcNPV-WT); Lane 5 shows the results of viral particles of a recombinant baculovirus (AcNPV-CAP-HA1/Vietnam) containing the HA1 gene of influenza virus H5N1/Vietnam/1203/04 strain and full-length gp64 gene inserted downstream of the dual promoter of the present invention; and Lane 6 shows the results of purified HA antigen of H5N1 (IT-003-0053p from Immune Technology). The baculoviruses were electrophoresed, and the presence of an expressed fusion product of the PfcSP gene and gp64 gene was checked. A strong band, indicating the presence of a fusion antigen of HA1 gene of H5N1/Vietnam/1203/04 and gp64 gene in the recombinant viral particles, was detected in Lane 5 of FIG. 2(B).

The above results of Example 4 show that a foreign gene having the desired immunogenicity and gp64 gene can be fused and expressed in recombinant viral particles of the recombinant baculovirus of the present invention produced by using the recombinant transfer vector of the present invention.

Example 5: Test of Expression of Vaccine Antigen from Recombinant Baculovirus of the Present Invention in Mammals

HepG2 cells were infected with AcNPV-Dual-PfMSP1-PfCSP at an infection multiplicity of 1. After 48 hours, the culture supernatant was removed, and the plate was rinsed with PBS three times. An acetone/ethanol solution (a mixed ratio of 7:3) cooled to -20°C was added to immobilize the cells at -20°C for 5 minutes.

A 5% normal goat serum (from Sigma) was added to perform blocking at room temperature for 1 hour. To detect the expression of PfCSP, an anti-PfCSP antibody (2A10, MR-4) labeled with Alexa Flour 594 was added; and to detect the expression of PfMSP-1₁₉, an anti-PfMSP-1₁₉ antibody (5.2, MR-4) and then an anti-mouse antibody labeled with FITC were added. After incubation, the reacted cells were detected under a fluorescence microscope.

FIG. 3 shows the results.

FIG. 3 shows HepG2 cells stained with a fluorescence-labeled antibody, which indicates that an antigen has been expressed from a recombinant baculovirus containing a fusion gene of the PfMSP1 gene and PfCSP gene in the HepG2 cells. The results of FIG. 3 (A) confirmed that a PfCSP antigen has been expressed. The results of FIG. 3 (B) confirmed that a PfMSP-1₁₉ antigen has been expressed. It was thus confirmed that fusion antigens can be expressed in mammalian cells. The results of FIG. 3 (A) and (B) clearly show that the recombinant baculovirus produced by using the transfer vector containing the dual promoter of the present invention can express the desired antigen in mammalian cells.

This suggests that when the recombinant baculovirus produced using the recombinant transfer vector of the present invention is administered to humans and other mammals, the virus particles enter the mammalian cells, and a mammalian promoter operates to produce a fusion product of the desired foreign antigen gene and gp64 gene in the mammalian cells, thus inducing the acquired immunity.

Example 6: Induction of Antibody by PfCSP Antigen Recombinant Virus and H5N1/HA1 Antigen Recombinant Virus

1. Inoculation of Virus Solution

Virus solutions of AcNPV-WT, AcNPV-CAP-PfCSP, AcNPV-CAP-PfCSP/467, AcNPV-CAP-HA1/Anhui, and AcNPV-CAP-HA1/Vietnam concentrated by ultracentrifugation were inoculated into the thigh muscles of BALB/c female mice in an amount of 1×10^8 PUF twice at two week-intervals.

2. Measurement of Antibody Titers

The mice were euthanized two weeks after the final immunization, and sera were collected from the mice and used for measuring antigen-specific antibody titers. Induction of PfcSP antigen-specific antibody titers by AcNPV-CAP-PfcSP and AcNPV-CAP-PfcSP/467 was measured by ELISA using a plate on which (NANP)₄NVDPC peptide (from Sigma), i.e., B-cell epitope of PfcSP, had been immobilized. Induction of H5N1/HA antigen-specific antibody titers by AcNPV-CAP-HA1/Anhui and AcNPV-CAP-HA1/Vietnam was measured by ELISA using a plate on which purified HA antigen of H5N1 virus (IT-003-005p from Immune Technology) had been immobilized. The absorbance at OD450 nm was measured using MaxiSorp (from NUNC) as the ELISA plate, HRP-labeled goat anti-mouse IgG (H&L) antibody (from American Qualex) as the secondary antibody, and TMB (from Calbiochem) for the color reaction.

FIG. 4 shows the results.

FIG. 4 (A) is a graph plotting the average absorbance of each group at OD450 nm obtained when the mouse sera were subjected to two-fold serial dilution from 800-fold to 102,400-fold dilutions. In the groups inoculated with PBS and AcNPV-WT, whose sera contained no antibody to the antigen, absorbance of even the 800-fold dilutions was 0.1 or less, indicating low reactivity. In contrast, in the groups inoculated with AcNPV-CAP-PfcSP and AcNPV-CAP-PfcSP/467, absorbance of the 800-fold dilutions was 1.138 and 1.878, respectively, indicating strong reactivity and clearly showing that antigen-specific antibodies were induced. FIG. 4 (B) is a graph plotting the average absorbance of each group at OD450 nm obtained when the mouse sera were subjected to two-fold serial dilution from 400-fold to 25,600-fold dilutions. In the groups inoculated with PBS and AcNPV-WT, whose sera contained no antibody to the antigen, absorbance of the 400-fold dilutions was 0.1 or less, indicating low reactivity. In contrast, in the group inoculated with AcNPV-CAP-HA1/Anhui and AcNPV-CAP-HA1/Vietnam, absorbance of the 3,200-fold dilution was 1.551 and 2.503, respectively, indicating strong reactivity and clearly showing that antigen-specific

antibodies were induced. FIG. 4 clearly shows that the recombinant baculovirus produced using a transfer vector containing the dual promoter of the present invention can induce an antibody to the desired antigen in mammals.

5 3. Measurement of Neutralization Value

 A hemagglutination inhibition (HI) test was performed using a mouse serum inoculated with AcNPV-CAP-HA1/Anhui. More specifically, the test was performed according to the method described in the instructions packaged with an influenza HI reagent "Seiken" (from Denka Seiken Co., Ltd.), using purified HA antigen of H5N1 virus (IT-003-0053p from Immune Technology). Absorption of non-specific agglutinins was performed using erythrocyte, and removal of non-specific agglutination inhibitors was performed using RDE (II) of "Seiken" (from Denka Seiken Co., Ltd.). The HI test was performed in the following manner. 0.025 mL of 10-fold diluted antiserum in a 96-well plate was subjected to 2-fold serial dilution using a diluent. To each well of the 96-well plate containing the diluted antiserum, 0.025 mL of HA antigen of H5N1 virus diluted to obtain an HA titer of 4 per 0.025 mL thereof was added. The plate was allowed to stand at room temperature for 30 minutes. 0.05 mL of an erythrocyte suspension for the reaction was added and stirred well. The mixture was allowed to stand at room temperature for 60 minutes. The final dilution of the test sample at which hemagglutination was completely inhibited was defined as the HI antibody titer.

 The results show that the sera inoculated with PBS and AcNPV-WT had HI antibody titers of 10 or less, whereas the serum inoculated with AcNPV-CAP-HA1/Anhui had an HI antibody titer of 40.

30 The results seem to indicate that when administered to humans and other mammals, the recombinant baculovirus produced from the recombinant transfer vector of the present invention can induce an antibody effective to the desired foreign antigen gene, thus providing vaccine effects.

35 Sequence Listing Free Text

SEQ ID NOS: 1 and 2 are the sequences of primers phsp65-F1 and phsp65-R1 for PCR of genomic DNA of *M. tuberculosis* H37Rv.

5 SEQ ID NOS: 3 and 4 are the sequences of primers phsp65-F2 and phsp65-R2 for PCR with pcDNA-hps65 as a template.

SEQ ID NOS: 5 and 6 are the sequences of primers pPolh-F2 and pgp64-R2 for PCR with pBACsurf-1 as a template to produce a gp64 gene DNA fragment.

10 SEQ ID NOS: 7 and 8 are the sequences of primers HA-f and HA-r for PCR to produce an influenza virus HA gene fragment.

SEQ ID NOS: 9 and 10 are the sequences of primers pHA-F1 and pHA-R1 for PCR with pCR-Blunt-HA as a template.

15 SEQ ID NOS: 11 and 12 are the sequences of primers Polh-f RsrII and GP64-r DraIII for PCR with pBACsurf-HA1 as a template.

SEQ ID NOS: 13 and 14 are the sequences of primers NP-f EcoRI and NP-r Cfr9I for RT-PCR of genomic RNA of influenza virus PR/8/34 strain.

20 SEQ ID NOS: 15, 16, and 12 are the sequences of primers gp64(272)-f, gp64(467)-f, and GP64-r DraIII for PCR of pCAP-H1N1/HA1-gp64.

SEQ ID NOS: 17 and 18 are the sequences of primers PfcSP-f(19) and PfcSP-r(373) for PCR with *P. falciparum* genomic DNA as a template.

25 SEQ ID NOS: 19 and 20 are the sequences of primers pAMA-F1 and pAMA1-R1 for PCR with *P. berghei* genomic DNA as a template.

30 SEQ ID NOS: 21 and 22 are the sequences of primers pPfcSP-F1 and pPfcSP-R1 for PCR with *P. falciparum* genomic DNA as a template.

SEQ ID NOS: 23 and 24 are the sequences of primers pPfs25-F1 and pPfs25-R2 for PCR with *P. falciparum* genomic DNA as a template.

35 SEQ ID NOS: 25 and 26 are the sequences of primers pPfMSP119-F1 and pPfMSP119-R2 for PCR with *P. falciparum* genomic

DNA as a template.

SEQ ID NOS: 17 and 27 are the sequences of primers PfcSP-f(19) and PfcSP-r(373 A361E) for PCR with pCAP-PfcSP as a template.

5 SEQ ID NOS: 28 and 27 are the sequences of primers PfcSP-f(76) and PfcSP-r(373 A361E) for PCR with pCAP-PfcSP as a template.

10 SEQ ID NO: 29 is the sequence of an artificial gene (PfcSP+) produced from the amino acid sequence of the PfcSP of *P. falciparum* 3D7 strain (in which, however, the A at the 361-position was replaced by E) using codons frequently used in Sf9 and human cells.

15 SEQ ID NOS: 30 and 31 are the sequences of primers PfcSP-f(+209) and PfcSP-r(+A361E) for PCR with PfcSP+ as a template.

SEQ ID NOS: 32, 33, 34 and 31 are the sequences of primers PfcSP-f(+76), PfcSP-r(+128), PfcSP-f(+209) BamHI, and PfcSP-r(+A361E) for PCR with PfcSP+ as a template.

20 SEQ ID NO: 35 is the sequence of an artificial gene produced from the amino acid sequence of the HA1 region of the hemagglutinin of influenza virus H5N1/Anhui/1/05 using codons frequently used in Sf9 and human cells.

25 SEQ ID NOS: 36 and 37 are the sequences of primers AH-F1 (5'-CAGTCTGCAGGACCAGATTTGCATC-3': (SEQ ID NO: 36); the PstI site is underlined) and AH-R4 (5'-CAGTCCCGGGCTCTCTTGCCTGC-3': (SEQ ID NO: 37); the XmaI site is underlined) for PCR with the artificial gene sequence of SEQ ID NO: 35 as a template.

30 SEQ ID NO: 38 is the sequence of an artificial gene produced from the amino acid sequence of the HA1 region of the hemagglutinin of influenza virus H5N1/Vietnam/1203/04 using codons frequently used in Sf9 and human cells.

35 SEQ ID NOS: 39 and 40 are the sequences of primers VN-F1 (5'-CAGTCTGCAGGACCAGATCTGTATC-3': (SEQ ID NO: 39); the PstI site is underlined), and VN-R4 (5'-CAGTCCCGGGCTCTCTTCTTCTTCTGC-3': (SEQ ID NO: 40); the XmaI site is underlined) for PCR with the

artificial gene sequence of SEQ ID NO: 38 as a template.

SEQ ID NOS: 41, 42, 43, 44, and 12 are the sequences of primers gp64(51)-f (5'-GACTCCCCGGGTGGAAATCACCATCGTGGAGACG-3': (SEQ ID NO: 41); the XmaI site is underlined), gp64(101)-f (5'-
5 GACTCCCCGGGATTTGCTTATGTGGAGCATCAGG-3': (SEQ ID NO: 42); the XmaI site is underlined), gp64(154)-f (5'-
GACTCCCCGGGCGCACCACACGTGCAACAAATCG-3': (SEQ ID NO: 43); the XmaI site is underlined), gp64(201)-f (5'-
GACTCCCCGGGACACTGTGCTTCATCGAGACGGC-3': (SEQ ID NO: 44); the XmaI
10 site is underlined), and GP64-r DraIII (5'-
GGGCACTTAGTGATATTGTCTATTACGGTTTCTAATC-3' (SEQ ID NO: 12); the
DraIII site is underlined).

SEQ ID NO: 45 is the sequence of an artificial gene produced from the amino acid sequence of the HA1 region of the
15 hemagglutinin of influenza virus H5N1/Anhui/1/05 by codon optimization using Gene Designer available from DNA2.0, Inc.

SEQ ID NOS: 46, 47, 48, 49, and 50 are the sequences of AH17-F (5'-GACTCTGCAGGATCAGATCTGTATTGGGTACC-3': (SEQ ID NO: 46); the PstI site is underlined, and AH345-R (5'-
20 CGATCCCCGGGCTCTCTTTCTCCTCCGCTCGC-3': (SEQ ID NO: 47); the XmaI site is underlined), AH410-R (5'-
CGATCCCCGGGCGGCCTCGAACTGGGTGTTTCATT-3': (SEQ ID NO: 48); the XmaI site is underlined), AH473-R (5'-
CGATCCCCGGGCGTCTCTGAGTTGAAGGCGCAC-3': (SEQ ID NO: 49); the XmaI
25 site is underlined, and AH520-R (5'-
CGATCCCCGGGCACCACTAATTTCTCTCGCTTC-3': (SEQ ID NO: 50); the XmaI site is underlined) for PCR with the artificial gene sequence of
SEQ ID NO: 45 as a template.

SEQ ID NO: 51 is the sequence of an artificial gene produced from the amino acid sequence of the HA1 region of the
30 hemagglutinin of influenza virus H5N1/Vietnam/1203/04 by codon optimization using Gene Designer available from DNA2.0, Inc.

SEQ ID NOS: 52, 53, 54, 55, and 56 are the sequences of primers VN17-F (5'-GACTCTGCAGGATCAGATCTGTATCGGATATC-3': (SEQ
35 ID NO: 52); the PstI site is underlined), and VN346-R (5'-

CGATCCCCGGGCCCCGCTTTTTCCTCCTCCGTTTCG-3': (SEQ ID NO: 53); the XmaI site is underlined), VN410-R (5'-

CGATCCCCGGGCCTCAAACCTGCGTATTCATTTTG-3': (SEQ ID NO: 54); the XmaI site is underlined), VN473-R (5'-

5 CGATCCCCGGGCTCTAAGCTGGAGCCTGACTTTGTC-3': (SEQ ID NO: 55); the XmaI site is underlined), and VN520-R (5'-

CGATCCCCGGGCACTAATCTCCTCTCTTTTAAGTC-3': (SEQ ID NO: 56); the XmaI site is underlined) for PCR with the artificial gene sequence of SEQ ID NO: 51 as a template.

10 SEQ ID NO: 57 is the sequence of an artificial gene produced from the amino acid sequence of the CSP of *Plasmodium falciparum* 3D7 strain by codon optimization using Gene Designer available from DNA2.0, Inc.

SEQ ID NOS: 58, 59, 60, 61, and 62 are the sequences of primers PfcSP_opt-f (5'-GACTCTGCAGATGATGCGAAAATTGGCCATACTG-3': (SEQ ID NO: 58); the PstI site is underlined), PfcSP_opt-r (397) (5'-CGATCCCCGGGCATTGAGGAACAGAAAGGAAAGAACCATG-3': (SEQ ID NO: 59); the XmaI site is underlined), PfcSP_opt-f (19) (5'-GACTCTGCAGCTGTTTCAGGAATACCACTGCTATGG-3': (SEQ ID NO: 60); (the PstI site is underlined), PfcSP_opt-r(373) (5'-CGATCCCCGGGCCTTCTCCATCTTACAAATTTTCTTTTCAATATCATTAGC -3': (SEQ ID NO: 61); (the XmaI site is underlined), PfcSP_opt-f (76) (5'-GACTCTGCAGGACGACGGAATAATGAGGACAACG-3': (SEQ ID NO: 62); the PstI site is underlined), and PfcSP_opt-f (205) (5'-GACTCTGCAGAATGCAAACCCAAATGCCAATCCAAACGC-3': (SEQ ID NO: 63); the PstI site is underlined) for PCR with the artificial gene sequence of SEQ ID NO: 57 as a template.

SEQ ID NOS: 64, 65, 66, and 67 are the sequences of primers gp64-p-f (5'-GACTCGGACCGGCCAGATAAAAAATAATCTTATCAATTAAG-3': (SEQ ID NO: 64); the RsrII site is underlined), gp64-p-r (5'-CGATACTAGTAGCACTGAGGCTTCTTATATACCCG-3': (SEQ ID NO: 65); the SpeI site is underlined), and vp39-p-f (5'-GACTCGGACCGCGTCGTACAAATCGAAATATTGTTGTG-3': (SEQ ID NO: 66); the RsrII site is underlined), and vp39-p-r (5'-CGATACTAGTGTGATTGAGAAAGAAATCTCTTATTC-3': (SEQ ID NO: 67); the

SpeI site is underlined) for PCR with Baculovirus genomic DNA as a template.

SEQ ID NOS: 68 and 69 are the sequences of primers
VSV-G-f (5'-GACTCCCCGGGCGTTCGAACATCCTCACATTCAAG -3' (SEQ ID NO:
5 68); the XmaI site is underlined), and VSV-G-r (5'-
GACTCACTTAGTGCTTTCCAAGTCGGTTCATCTC-3': (SEQ ID NO: 69); the
DraIII site is underlined) for PCR with pVSV-G as a template.

CLAIMS

1. A pharmaceutical composition comprising a recombinant *Autographa californica* nucleopolyhedrosis virus (AcNPV) as an active agent and, optionally, a pharmaceutically acceptable carrier,

wherein the recombinant AcNPV contains a gene structure having a fusion gene of

(A) a gene encoding a partial amino acid sequence of SEQ ID NO:70 (*Plasmodium falciparum* CircumSporozoite Protein; PfCSP), and

(B) a gene encoding a partial amino acid sequence of gp64 viral particle protein (gp64) encoded in the AcNPV genome having the nucleotide sequence of GenBank Accession No. L22858 as of August 07, 2007, which is described below, under the control of a dual promoter comprising Polyhedrin promoter and CAG promoter linked to each other (CAP); and

wherein the recombinant AcNPV is selected from the group consisting of:

(1) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 19-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 21-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-PfCSP),

(2) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 19-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 467-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-PfCSP/467),

(3) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 205-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 21-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-CO/205),

(4) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 76-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 467-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-CO/76/467),

(5) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 76-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 21-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-CO/76),

(6) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 1-397 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 21-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-CO/full),

(7) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 205-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence

consisting of amino acids 467-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-CO/205/467),

(8) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 19-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 467-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-CO/19/467),

(9) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 19-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 21-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-CO/19),

(10) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 1-397 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 467-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-CO/full/467),

(11) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 209-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 467-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-PfCSP+209/467), and

(12) a recombinant AcNPV which contains a gene encoding an amino acid sequence consisting of amino acids 76-128, and 209-373 of SEQ ID NO:70 as a gene of (A), and a gene encoding an amino acid sequence consisting of amino acids 467-512 of GenBank Accession No. L22858 as a gene of (B) (AcNPV-CAP-PfCSP+76/209/467).

<GenBank Accession No. L22858 as of August 07, 2007>

1 gaattctacc cgtaaagcga gtttagtttt gaaaaacaaa tgacatcatt
tgtataatga

61 catcatcccc tgattgtgtt ttacaagtag aattctatcc gtaaagcgag
ttcagttttg

121 aaaacaaatg agtcatacct aaacacgtta ataatcttct gatatcagct
tatgactcaa

181 gttatgagcc gtgtgcaaaa catgagataa gtttatgaca tcatccactg
atcgtgcgtt

241 acaagtagaa ttctactcgt aaagccagtt cggttatgag ccgtgtgcaa
aacatgacat

301 cagcttatga ctcatacttg attgtgtttt acgcgtagaa ttctactcgt
aaagcgagtt

361 cggttatgag ccgtgtgcaa aacatgacat cagcttatga gtcataatta
atcgtgcgtt

421 acaagtagaa ttctactcgt aaagcgagtt gaaggatcat atttagttgc
gtttatgaga

481 taagattgaa agcacgtgta aaatgtttcc cgcgcgttgg cacaactatt
tacaatgcgg

541 ccaagttata aaagattcta atctgatatg ttttaaaaca cctttgcggc
ccgagttggt

601 tgcgtacgtg actagcgaag aagatgtgtg gaccgcagaa cagatagtaa
aacaaaaccc

661 tagtattgga gcaataatcg atttaaccaa cacgtctaaa tattatgatg

gtgtgcattt

721 tttgcgggcg ggcctgttat acaaaaaaat tcaagtacct ggccagactt
tgccgcctga

781 aagcatagtt caagaattta ttgacacggt aaaagaattt acagaaaagt
gtcccggcat

841 gttggtgggc gtgactgca cacacggtat taatcgcacc ggttacatgg
tgtgcagata

901 tttaatgcac accctgggta ttgcgccgca ggaagccata gatagattcg
aaaaagccag

961 aggtcacaaa attgaaagac aaaattacgt tcaagattta ttaatttaat
taatattatt

1021 tgcattcttt acaaaatact ttatcctatt ttcaaattgt
tgcgcttctt ccagcgaacc

1081 aaaactatgc ttcgcttgct ccgtttagct tgtagccgat
cagtggcggt gttccaatcg

1141 acggtaggat taggccggat attctccacc acaatgttgg
caacggtgat gttacgttta

1201 tgcttttggt tttccacgta cgtcttttgg ccggtaatag
ccgtaaactg agtgccgctg

1261 cgcgtcacgc acaacaccgg atgtttgcgc ttgtccgcgg
ggtattgaac cgcgcatcc

1321 gacaaatcca ccactttggc aactaaatcg gtgacctgcg
cgtctttttt ctgcattatt

1381 tcgtctttct tttgcatggt ttcctggaag ccggtgtaca
tgcggttttag atcagtcatt

1441 acgcgcgtga cctgcaaact tttggcctcg atctgcttgt
ccttgatggc aacgatgcgt

1501 tcaataaact cttgtttttt aacaagttcc tcggtttttt
gcgccaccac cgcttgacgc

1561 gcgtttgtgt gctcgggtgaa tgtcgcaact agcttagtca
ccaactgttt gctctcctcc

1621 tcccgttggt tgatcgcggg atcgtacttg ccggtgcaga
gcacttgagg aattacttct

1681 tctaaaagcc attcttgtaa ttctatggcg taaggcaatt
tggaattcat aatcagctga

1741 atcacgccgg atttagtaat gagcactgta tgcggctgca
aatacagcgg gtcgcccctt

1801 ttcacgacgc tgtagaggt agggcccca ttttgatgg
tctgctcaaa taacgatttg

1861 tatttattgt ctacatgaac acgtatagct ttatcacaaa
ctgtatatatt taaactgtta

1921 gcgacgtcct tggccacgaa ccggacctgt tggtcgcgct
ctagcacgta ccgcagggtg

1981 aacgtatctt ctccaaattt aaattctcca attttaacgc
gagccatttt gatacacgtg

2041 tgtcgatttt gcaacaacta ttgtttttta acgcaaacta
aacttattgt ggtaagcaat

2101 aattaaatat gggggaacat gcgccgctac aacactcgtc
gttatgaacg cagacggcgc

2161 cggctcggc gcaagcggct aaaacgtgtt gcgcgttcaa
cgcggaac atcgcaaaag

2221 ccaatagtag agttttgatt tgcatattaa cggcgatttt

ttaaattatc ttattttaata

2281 aatagttatg acgcctacaa ctccccgccc gcgttgactc
gctgcacctc gagcagttcg

2341 ttgacgcctt cctccgtgtg gccgaacacg tcgagcgggt
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2401 ccgcacgcga cgcacaagta tctgtacacc gaatgatcgt
cgggcgaagg cacgtcggcc

2461 tccaagtggc aatattggca aattcgaaaa tatatacagt
tgggttggtt gcgcataatc

2521 atcgtggcgt tgggcatgta cgtccgaacg ttgatttgca
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2641 tcgcgcaatc gagtcaagtg atcaaagtgt ggaataatgt
tttctttgta ttcccagatc

2701 aagcgcagcg cgtatttttaa caaactagcc atcttgtaag
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2761 tttatccaat aatatattat gtatcgcacg tcaagaatta
acaatgcgcc cgttgtcgca

2821 tctcaacacg actatgatag agatcaaata aagcgcgaat
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gtaataagtt tttacgaagc

2941 gatgacatga cccccgtagt gacaacgatc acgccccaaa
gaactgccga ctacaaaatt

3001 accgagtatg tcggtgacgt taaaactatt aagccatcca
atcgaccgtt agtcgaatca

3061 ggaccgctgg tgcgagaagc cgcgaagtat ggogaatgca
tcgtataacg tgtggagtcc

3121 gctcattaga gcgtcatggt tagacaagaa agctacatat
ttaattgatc ccgatgattt

3181 tattgataaa ttgaccctaa ctccatacac ggtattctac
aatggcgggg ttttggtcaa

3241 aatttccgga ctgcgattgt acatgctggt aacggctccg
cccactatta atgaaattaa

3301 aaattccaat tttaaaaaac gcagcaagag aaacatttgt
atgaaagaat gcgtagaagg

3361 aaagaaaaat gtcgtcgaca tgctgaacaa caagattaat
atgcctccgt gtataaaaaa

3421 aatattgaac gatttgaaag aaaacaatgt accgcgcggc
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3481 tataactaac tgttacattg caaacgtggt ttcgtgtgcc
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3541 aatcaaggct ctgacgcatt tctacaacca cgactccaag
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3601 tcttttaatc aaatcccaag atgtgtataa accaccaaac
tgccaaaaaa tgaaaactgt

3661 cgacaagctc tgtccgtttg ctggcaactg caagggtctc
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3781 acaagaacat ttgtagtatt atctataatt gaaaacgcgt

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agacccaacc gttgttacia
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6481 ggggtgggtg aattcaatat tataattgga atacaaatcg
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cgctcaatgt aagcaattgt
6601 attgtaaaga gattgtctca agctcggatc ccgcacgccg
ataacaagcc ttttcatttt
6661 tactacagca ttgtagtggc gagacacttc gctgtcgtcg
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6781 tgtgttgtcg taaatgttgt ttttgataat ttgcgcttcc
gcagtatcga cacgttcaaa
6841 aaattgatgc gcatcaattt tgttggtcct attattgaat
aaataagatt gtacagattc
6901 atatctacga ttcgtcatgg ccaccacaaa tgctacgctg

caaacgctgg tacaatttta
6961 cgaaaactgc aaaaacgtca aaactcggta taaaataatc
aacgggcgct ttggcaaaat
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2. A pharmaceutical composition of claim 1, which is a vaccine.

3. A pharmaceutical composition of claim 1, which is a malaria vaccine.