(CHO) cells and formulated in the adjuvant MF59. Another developed by Glaxo-Smithkline (GSK) contains a truncated gD2 formulated with adjuvants alum and 3-O-deacylated monophosphoryl lipid A (MPL). Both vaccines were immunogenic and well tolerated in phase I/II trials. However in phase III analyses, the Chiron vaccine showed no overall efficacy against HSV-2 seroconversion and work was discontinued. The GSK vaccine showed significant efficacy (73-74%) in HSV-1, HSV-2 seranegative women volunteers but no efficacy in men.

While even limited vaccine efficacy would beneficially impact HSV sufferers, these trials are testing only a small number of vaccine possibilities. This is because the vaccine discovery has not been systematic. Pursuance of a whole-virus vaccine assumes that presentation of the pathogen itself to the immune system will generate optimal immunity. Indeed the breadth and duration of immune responses to whole pathogen vaccines historically have been better than subunit vaccines. However, pathogenicity of the vaccine strain must be considered. Subunit vaccines, to date, have been selected for vaccine testing based on their assumed importance in disease pathogenesis and immunogenicity during infection. These approaches have identified one candidate against HSV with limited efficacy in some but no efficacy in other formulations. Thus, new and improved methodologies for herpesvirus vaccine discovery are needed to protect against herpes diseases.

~~II.~~ Summary ~~of the Invention~~

Infection and transmission of HSV-2 is a major health concern. The present disclosure provides, *inter alia*, certain highly effective vaccines against HSV-2. Such vaccines can be used either therapeutically or prophylactically. The present disclosure also provides specific antigens and methods for using the antigens to elicit an immune response against HSV-2.

In a first aspect, there is provided a vaccine formulation comprising a pharmaceutically-acceptable carrier and an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of a transmembrane domain.

In a second aspect, there is provided a vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide comprising the amino acid sequence of SEQ ID NO:5 having an internal deletion of 8-23 contiguous amino acid residues selected from amino acid residues 340-363 of SEQ ID NO:5.

In a third aspect, there is provided a vaccine formulation comprising a pharmaceutically acceptable carrier and a polypeptide comprising the amino acid sequence of SEQ ID NO:4.

In a fourth aspect, there is provided a vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide comprising the amino acid sequence of SEQ ID NO:4 having a deletion of 1-20 amino acid residues at the N-terminus, C-terminus, or both, of SEQ ID NO:4.

In a fifth aspect, there is provided a vaccine formulation comprising a pharmaceutically-acceptable carrier, an adjuvant comprising one or more purified fractions of quillaja saponins, a first polypeptide comprising the amino acid sequence of SEQ ID NO:4 and a second polypeptide comprising the amino acid sequence of SEQ ID NO:1 or an immunogenic fragment comprising at least 8 contiguous amino acids of SEQ ID NO:1.

In a sixth aspect, there is provided a vaccine formulation comprising a pharmaceutically-acceptable carrier, a first polypeptide comprising the amino acid sequence of SEQ ID NO:4, and a second polypeptide comprising the amino acid sequence of SEQ ID NO:2.

In one ~~aspect~~embodiment, the present disclosure describes a vaccine formulation comprising a pharmaceutical-acceptable carrier and at least one polypeptide consisting of SEQ ID NOS: 2, 3, 4 and 5 or an immunogenic fragment thereof, and optionally further comprising SEQ ID NO:1 or an immunogenic fragment thereof.

The vaccine formulation may comprise a first polypeptide consisting of one of the above SEQ ID NOS, and a second polypeptide consisting of another one of the above SEQ ID NOS.

Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a vaccine formulation comprising a pharmaceutically acceptable carrier, an adjuvant comprising one or more purified fractions of quillaja saponins, and at least one polypeptide comprising any of SEQ ID NOS: 2, 3, 4 and 5 or an immunogenic fragment thereof, and optionally further comprising SEQ ID NO:1 or an immunogenic fragment thereof.

A further ~~aspect~~embodiment of the present ~~invention~~disclosure provides a vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide consisting of SEQ ID NO: 2 or an immunogenic fragment thereof. Residues may be truncated from SEQ ID NO:2. The polypeptide may be glycosylated, or may be unglycosylated.

In still a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide comprising SEQ ID NO:5, wherein the polypeptide lacks all or at least an 8 contiguous amino acid residue portion of the transmembrane domain spanning residues 341-363. Accordingly, one ~~aspect~~embodiment of the present ~~invention~~disclosure provides a vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide comprising SEQ ID NO:4. The polypeptide may be glycosylated, or may be unglycosylated.

Still another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a vaccine formulation comprising a pharmaceutically-acceptable carrier, a polypeptide comprising SEQ ID NO:5. The polypeptide may be glycosylated, or may be unglycosylated.

Yet another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a vaccine formulation comprising a pharmaceutically-acceptable carrier, a polypeptide comprising SEQ ID NO:3. The polypeptide may be glycosylated, or may be unglycosylated.

In some embodiments, polypeptides in the vaccine formulations that may be conjugated to an immunogenic carrier, for example keyhole limpet hemocyanin. In other embodiments, the vaccine formulations further comprise an adjuvant. The adjuvant may be one or more purified fractions of quillaja saponins.

The present ~~invention~~disclosure provides methods or treating a subject suffering from or susceptible to HSV-2 infection by administering an effective amount of a vaccine formulation disclosed herein. In some embodiments, the method inhibits HSV-2 symptoms, for example by reducing the number of herpetic lesions, reducing the number of days a subject experiences herpetic lesions, reducing infection by HSV-2 in an uninfected subject, increasing the IgG titer and/or T cell response to one or more HSV-2 antigens, and/or reducing the number of herpetic lesions at the onset of HSV-2 infection.

In another ~~aspect~~embodiment, the present disclosure describes the results of a high-throughput system for in vitro screening of libraries of efficacious T cells to identify their specific target antigens from the complete proteome of HSV-2. This technology allowed the identification of individual antigens, likely to be effective in vivo, as either a prophylactic or therapeutic composition. In one ~~aspect~~embodiment, herein are provided several critical protective T cell antigens that can be incorporated into protein-based compositions that elicit an immune response.

One ~~aspect~~embodiment of the present ~~invention~~disclosure provides pharmaceutical compositions comprising two or more isolated polypeptides selected from polypeptides having an amino acid sequence of at least one of SEQ ID NOS: 1-38, or an immunogenic fragment thereof.

In another ~~aspect~~embodiment, the present ~~invention~~disclosure provides vaccine formulations that include a pharmaceutically-acceptable carrier and a polypeptide comprising at least one of SEQ ID NOS: 1-38, or an immunogenic fragment thereof. In certain embodiments, the polypeptide consists of at least one of SEQ ID NOS: 1-38.

Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of inducing an immune response in a subject, comprising administering to said subject an effective amount of a vaccine formulation or a pharmaceutical composition comprising an effective amount of two or more isolated polypeptides selected from polypeptides having an amino acid sequence of at least one of SEQ ID NOS: 1-38, or an immunogenic fragment thereof.

Yet another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of reducing one or more symptoms of HSV-2 infection in a subject, comprising administering to

said subject an effective amount of a vaccine formulation or a pharmaceutical composition comprising two or more isolated polypeptides selected from polypeptides having an amino acid sequence of at least one of SEQ ID NOS: 1-38, or an immunogenic fragment thereof. In some embodiments, the symptoms of HSV-2 infection comprise one or more of lesion formation, pain, irritation, itching, fever, malaise, headache, viral shedding, and prodrome.

A further ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of inhibiting the onset of HSV-2 infection, comprising administering an effective amount of a vaccine formulation or a composition comprising two or more isolated HSV polypeptides selected from polypeptides having an amino acid sequence of at least one of SEQ ID NOS: 1-38, or an immunogenic fragment thereof.

Applicants disclose another ~~aspect~~embodiment of the present ~~invention~~disclosure, which provides a method of inhibiting development of a latent HSV-2 infection in a subject exposed to HSV-2, comprising administering an effective amount of a vaccine formulation or a composition comprising two or more isolated HSV-2 polypeptides selected from polypeptides having an amino acid sequence of at least one of SEQ ID NOS: 1-38, or an immunogenic fragment thereof.

In a related ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of reducing viral shedding in a subject infected with HSV-2, comprising administering an effective amount of a vaccine formulation or a composition comprising two or more isolated HSV-2 polypeptides selected from polypeptides having an amino acid sequence of at least one of SEQ ID NOS: 1-38, or an immunogenic fragment thereof.

Further, an ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of reducing recurrence of outbreaks in a subject infected with HSV-2, comprising administering an effective amount of a vaccine formulation or a composition comprising two or more isolated HSV-2 polypeptides selected from polypeptides having an amino acid sequence of at least one of SEQ ID NOS: 1-38, or an immunogenic fragment thereof.

An additional ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of producing any of the pharmaceutical compositions described above, comprising expressing said two or more polypeptides; and isolating said two or more polypeptides.

Applicants further disclose an ~~aspect~~embodiment of the present ~~invention~~disclosure which provides a method for diagnosing severity of symptoms in a subjected infected with HSV-2, comprising (i) measuring activation of T cells in response to autologous antigen presenting cells (APC) pulsed with one or more isolated HSV-2 polypeptides selected from polypeptides set forth in SEQ ID NOS: 1-38, or an immunogenic fragment thereof, and (ii) comparing said levels to reference levels obtained from infected subjects experiencing frequent outbreaks; whereby a significant increase in said responses relative to reference levels indicates that said subject has less severe symptoms (e.g., the subject is asymptomatic). A significant increase in response can, for example, comprise a 1.5-fold or greater, 2-fold or greater, 3-fold or greater, 5-fold or greater, 10-fold or greater or even 20-fold or greater increase.

Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method for diagnosing severity of symptoms in a subjected infected with HSV-2, comprising (i) measuring activation of T cells from naturally infected or virus-exposed subjects in response to APC presenting one or more isolated HSV-2 polypeptides selected from polypeptides set forth in SEQ ID NOS: 1-38, or an immunogenic fragment thereof, and (ii) comparing said levels to reference levels obtained from infected subjects experiencing frequent outbreaks; whereby a significant decrease in said activation relative to reference levels indicates that said subject has more severe symptoms (e.g., frequent outbreaks).

Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides pharmaceutical compositions comprising an antibody that binds to one or more isolated HSV polypeptides selected from the list consisting of SEQ ID NOS: 1-38, or an immunogenic fragment thereof.

Moreover, a different ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of identifying immunogenic compositions for HSV-2 by testing two or more polypeptides selected from polypeptides having an amino acid sequence of any one of SEQ ID NOs. 1-38, or an immunogenic fragment thereof, for ability to promote cytokine production in a mammalian T cell, wherein an immunogenic composition is one that elevates levels of a cytokine significantly above the levels of that cytokine produced by a naïve mammalian T cell. A significant increase in cytokine

levels is typically one that is at least 1.5-fold, 2-fold, 3-fold, 5-fold, 10-fold or even 20-fold the level produced by a naïve cell.

Still another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of detecting HSV-2 in a sample from a subject, said method comprising (i) contacting said sample with one or more antibodies raised against one or more polypeptides having an amino acid sequence of SEQ ID NOS: 1-38 or an immunogenic fragment thereof, and (ii) detecting said one or more antibodies bound to said one or more HSV-2 polypeptide from the sample.

Finally, one ~~aspect~~embodiment of the present ~~invention~~disclosure provides pharmaceutical compositions comprising two or more isolated polynucleotides, selected from nucleotide SEQ ID NOS: 1-38, or fragments encoding immunogenic peptides thereof.

III. Brief Description of the Drawings

Figures 1A and B are graphs showing, respectively, $CD4^+$ and $CD8^+$ T cell responses following immunization with gD2 full-length protein, gD2ΔTMR, or gD2 truncated immediately upstream of the transmembrane domain (denoted 306t).

Figures 2A and B are graphs showing, respectively, $CD4^+$ and $CD8^+$ T cell responses following immunization with pooled, overlapping peptides spanning gL2, ICP4.1, or ICP4 fragments encoded by RS1.1, RS1.3.1 and RS1.3.2.

Figure 3A and B are graphs showing, respectively, $CD4^+$ and $CD8^+$ T cell responses following immunization with gD2ΔTMR, or gD2ΔTMR and ICP4.2.

IV. Detailed Description

This application describes vaccines and immunogenic compositions against HSV-2. Vaccine formulations may include a polypeptide comprising a sequence from Table 1 or an immunogenic fragment thereof, or a combination of at least two polypeptides comprising sequences from Table 1 or immunogenic fragments thereof. In certain embodiments, the polypeptide(s) of the vaccines comprise the

Claims

1. A vaccine formulation comprising a pharmaceutical-acceptable carrier and at least one polypeptide consisting of SEQ ID NOS: 2, 3, 4 and 5 or an immunogenic fragment thereof, and optionally further comprising SEQ ID NO:1 or an immunogenic fragment thereof.

2. The vaccine formulation of claim 1, comprising a first polypeptide consisting of SEQ ID NO:1 and a second polypeptide consisting of SEQ ID NO:3 or SEQ ID NO:4.

3. The vaccine formulation of claim 1, comprising a first polypeptide consisting of SEQ ID NO:2 and a second polypeptide consisting of SEQ ID NO:3 or SEQ ID NO:4.

4. The vaccine formulation of claim 1, comprising a first polypeptide consisting of SEQ ID NO:3 and a second polypeptide consisting of SEQ ID NO: 4.

5. The vaccine formulation of claim 1, comprising a first polypeptide consisting of SEQ ID NO:1, a second polypeptide consisting of SEQ ID NO:3, and a third polypeptide consisting of SEQ ID NO:4.

6. The vaccine formulation of claim 1, comprising a first polypeptide consisting of SEQ ID NO:2, a second polypeptide consisting of SEQ ID NO:3, and a third polypeptide consisting of SEQ ID NO:4.

7. A vaccine formulation comprising a pharmaceutically acceptable carrier, an adjuvant comprising one or more purified fractions of quillaja saponins, and at least one polypeptide comprising any of SEQ ID NOS: 2, 3, 4 and 5 or an immunogenic fragment thereof, and optionally further comprising SEQ ID NO:1 or an immunogenic fragment thereof.

8. A vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide consisting of SEQ ID NO: 2 or an immunogenic fragment thereof.

9. The vaccine formulation of claim 8, wherein the fragment is a truncated fragment of SEQ ID NO:2 wherein from 1-20 amino acid residues are removed from the N-terminus, C-terminus, or both.

10. The vaccine formulation of claim 9, wherein the fragment is a truncated fragment of SEQ ID NO:2 wherein from 1-10 amino acid residues are removed from the N-terminus, C-terminus, or both.

11. A vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide comprising SEQ ID NO:5, wherein the polypeptide lacks all or at least 8 contiguous amino acid residues of the transmembrane domain spanning residues 341-363.

12. A vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide comprising SEQ ID NO:4.

13. A vaccine formulation comprising a pharmaceutically-acceptable carrier, a polypeptide comprising SEQ ID NO:5.

14. The vaccine formulation of claim 13, wherein the polypeptide is unglycosylated

15. A vaccine formulation comprising a pharmaceutically-acceptable carrier, a polypeptide comprising SEQ ID NO:3.

16. The vaccine formulation of any of claims 1, 8, 11, 13, or 15, wherein the at least one polypeptide is conjugated to an immunogenic carrier.

17. The vaccine formulation of any of claims 1, 8, 11, 13, or 15, further comprising an adjuvant.

18. The vaccine formulation of claim 17, wherein the adjuvant is one or more purified fractions of quillaja saponins.

19. The vaccine formulation of claim 18, wherein the adjuvant comprises saponin fraction A and saponin fraction C.

20. The vaccine formulation of claim 19, wherein the adjuvant comprises cholesterol, phosphatidyl choline, saponin fraction A and saponin fraction C.

21. The vaccine formulation of claim 20, wherein the adjuvant is in the form of particles.

22. The vaccine formulation of claim 21, wherein particles comprising saponin fraction A are substantially free of saponin fraction C and particles comprising saponin fraction C are substantially free of saponin fraction A.

23. The vaccine formulation of any of claims 1, 8, 11, 13, or 15, wherein the vaccine formulation comprises 5-200 μg of the at least one polypeptide and 5-200 μg of the adjuvant.

24. The vaccine of formulation of any of claims 1, 7, 8, 11, 13 or 15, wherein the polypeptide is a fusion protein further comprising a tag.

25. The vaccine formulation of any of claims 1-24, wherein the vaccine formulation inhibits HSV-2 symptoms.

26. The vaccine formulation of claim 25, wherein the vaccine formulation reduces the number of herpetic lesions.

27. The vaccine formulation of claim 25, wherein the vaccine formulation reduces the number of days a subject experiences herpetic lesions.

28. The vaccine formulation of any of claims 1-24, wherein the vaccine formulation inhibits infection by HSV-2 in an uninfected subject.

29. The vaccine formulation of claim 28, wherein the vaccine formulation increases the IgG titer to one or more HSV-2 antigens.

30. The vaccine formulation of claim 28, wherein the vaccine formulation increases the T cell response to one or more HSV-2 antigens.

31. The vaccine formulation of claim 28, wherein the vaccine formulation reduces the number of herpetic lesions at the onset of HSV-2 infection.

32. The vaccine formulation of any of claims 1-24, wherein the vaccine formulation inhibits HSV-2 symptoms or inhibits infection by HSV-2 in three or fewer doses.

33. A method for treating a subject suffering from or susceptible to HSV-2 infection, comprising administering an effective amount of a vaccine formulation according to claims 1-24.

34. The method of claim 33, wherein the method inhibits HSV-2 symptoms.

35. The method of claim 34, wherein the method reduces the number of herpetic lesions.

36. The method of claim 35, wherein the method reduces the number of days a subject experiences herpetic lesions.

37. The method of claim 33, wherein the method inhibits infection by HSV-2 in an uninfected subject.

38. The method of claim 37, wherein the method increases the IgG titer to one or more HSV-2 antigens.

39. The method of claim 37, wherein the method increases the T cell response to one or more HSV-2 antigens.

40. The method of claim 37, wherein the method reduces the number of herpetic lesions at the onset of HSV-2 infection.

41. The method of claim 33, wherein the method treats a subject within a three dose regimen.

42. The method of claim 33, wherein the subject is a human.

CLAIMS

The invention claimed is:

1. A vaccine formulation comprising a pharmaceutically-acceptable carrier and an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of a transmembrane domain.

2. The vaccine formulation of claim 1, further comprising an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of an HSV-2 ICP4 polypeptide.

3. A vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide comprising the amino acid sequence of SEQ ID NO:5 having an internal deletion of 8-23 contiguous amino acid residues selected from amino acid residues 340-363 of SEQ ID NO:5.

4. The vaccine formulation of claim 3, wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:5 having an internal deletion of 8-23 contiguous amino acid residues selected from amino acid residues 340-363 of SEQ ID NO:5.

5. The vaccine formulation of claim 3, further comprising a second polypeptide comprising an amino acid sequence having at least 90% identity to SEQ ID NO:1.

6. The vaccine formulation of claim 3, further comprising a second polypeptide comprising the amino acid sequence of SEQ ID NO:1 or an immunogenic fragment comprising at least 8 contiguous amino acids of SEQ ID NO:1.

7. The vaccine formulation of claim 5, wherein the second polypeptide consists of an amino acid sequence having at least 90% identity to SEQ ID NO:1.

8. The vaccine formulation of claim 6, wherein the second polypeptide consists of the amino acid sequence of SEQ ID NO:1 or an immunogenic fragment consisting of at least 8 contiguous amino acids of SEQ ID NO:1.

9. The vaccine formulation of claim 3, further comprising a second polypeptide comprising an amino acid sequence having at least 90% identity to SEQ ID NO:2.

10. The vaccine formulation of claim 3, further comprising a second polypeptide comprising the amino acid sequence of SEQ ID NO:2 or an immunogenic fragment comprising at least 8 contiguous amino acids of SEQ ID NO:2.

11. The vaccine formulation of claim 9, wherein the second polypeptide consists of an amino acid sequence having at least 90% identity to SEQ ID NO:2.

12. The vaccine formulation of claim 10, wherein the second polypeptide consists of the amino acid sequence of SEQ ID NO:2 or an immunogenic fragment consisting of at least 8 contiguous amino acids of SEQ ID NO:2.

13. A vaccine formulation comprising a pharmaceutically acceptable carrier and a polypeptide comprising the amino acid sequence of SEQ ID NO:4.

14. The vaccine formulation of claim 13, wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:4.

15. The vaccine formulation of claim 13, further comprising a second polypeptide comprising an amino acid sequence having at least 90% identity to SEQ ID NO:1.

16. The vaccine formulation of claim 13, further comprising a second polypeptide comprising the amino acid sequence of SEQ ID NO:1 or an immunogenic fragment comprising at least 8 contiguous amino acids of SEQ ID NO:1.

17. The vaccine formulation of claim 15, wherein the second polypeptide consists of an amino acid sequence having at least 90% identity to SEQ ID NO:1.

18. The vaccine formulation of claim 16, wherein the second polypeptide consists of the amino acid sequence of SEQ ID NO:1 or an immunogenic fragment consisting of at least 8 contiguous amino acids of SEQ ID NO:1.

19. The vaccine formulation of claim 13, further comprising a second polypeptide comprising an amino acid sequence having at least 90% identity to SEQ ID NO:2.

20. The vaccine formulation of claim 13, further comprising a second polypeptide comprising the amino acid sequence of SEQ ID NO:2 or an immunogenic fragment comprising at least 8 contiguous amino acids of SEQ ID NO:2.

21. The vaccine formulation of claim 19, wherein the second polypeptide consists of an amino acid sequence having at least 90% identity to SEQ ID NO:2.

22. The vaccine formulation of claim 20, wherein the second polypeptide consists of the amino acid sequence of SEQ ID NO:2 or an immunogenic fragment consisting of at least 8 contiguous amino acids of SEQ ID NO:2.

23. A vaccine formulation comprising a pharmaceutically-acceptable carrier and a polypeptide comprising the amino acid sequence of SEQ ID NO:4 having a deletion of 1-20 amino acid residues at the N-terminus, C-terminus, or both, of SEQ ID NO:4.

24. The vaccine formulation of any one of claim 5, 9, 15, or 19, further comprising a third polypeptide comprising SEQ ID NO:3 or an immunogenic fragment comprising at least 8 contiguous amino acids of SEQ ID NO:3.

25. A vaccine formulation comprising a pharmaceutically-acceptable carrier, an adjuvant comprising one or more purified fractions of quillaja saponins, a first polypeptide comprising the amino acid sequence of SEQ ID NO:4 and a second polypeptide comprising the amino acid sequence of SEQ ID NO:1 or an immunogenic fragment comprising at least 8 contiguous amino acids of SEQ ID NO:1.

26. A vaccine formulation comprising a pharmaceutically-acceptable carrier, a first polypeptide comprising the amino acid sequence of SEQ ID NO:4, and a second polypeptide comprising the amino acid sequence of SEQ ID NO:2.

27. The vaccine formulation of claim 28, wherein the first polypeptide consists of the amino acid sequence of SEQ ID NO:4 and the second polypeptide consists of the amino acid sequence of SEQ ID NO:2.

28. The vaccine formulation of claim 28 or 29, further comprising an adjuvant.