developed by Chiron and the other by GlaxoSmithKline, were both halted due to insufficient efficacy. Chiron's vaccine comprised truncated forms of two HSV-2 glycoproteins, gD2 and gB2, in combination with the adjuvant MF59. The vaccine at best provided transient protection against HSV-2 although high titers of antibodies to HSV-2 were generated (Stanberry, ibid). GlaxoSmithKline (GSK) developed and tested a similar vaccine; however it contained only a single glycoprotein, gD2, and alum and MPL as adjuvants. Following eight years of studies and clinical trials, GSK pronounced it as a failure in October 2010. The vaccine was unsuccessful in preventing infection in seronegative women, the only group in early clinical trials that had seemed to benefit.

SUMMARY

In one ~~embodiment~~ aspect of the disclosure, an immunogenic fragment of an HSV-2 polypeptide is provided selected from the group consisting of: (a) an immunogenic fragment of UL19 polypeptide lacking at least 75% of amino acids 1-450 of SEQ ID NO: 4 and lacking at least 75% of amino acids of 1055-1374 of SEQ ID NO: 4; (b) the sequence set out in SEQ ID NO: 12; (c) an immunogenic variant of (a) or (b) that retains at least 85% amino acid identity over at least 15 contiguous amino acids; (d) an immunogenic fragment of (a) or (b); and (e) a chimeric fusion of (a), (b), (c) or (d). In another embodiment an isolated polynucleotide encoding the aforementioned polypeptide is provided.

[0009] Pharmaceutical compositions are also provided by the instant disclosure. In one ~~embodiment~~aspect, an immunogenic, pharmaceutical composition is provided comprising: (i) an immunogenic fragment of an HSV-2 polypeptide selected from the group consisting of: (a) an immunogenic fragment of UL19 polypeptide lacking at least 75% of amino acids 1-450 of SEQ ID NO: 4 and lacking at least 75% of amino acids of 1055-1374 of SEQ ID NO: 4; (b) the sequence set out in SEQ ID NO: 12; (c) an immunogenic variant of (a) or (b) that retains at least 85% amino acid identity over at least 15 contiguous amino acids; (d) an immunogenic fragment of (a) or (b); and (e) a chimeric fusion of (a), (b), (c) or (d); (ii) optionally, an agent that activates innate immunity; and (iii) a pharmaceutically acceptable carrier.

[0010] In another embodiment, the aforementioned composition is provided which further comprises UL25 or an immunogenic fragment thereof. In still another embodiment, the composition further comprises gD2 or an immunogenic fragment thereof.

[0011] In still another embodiment of the instant disclosure, the aforementioned composition is provided wherein the agent is an adjuvant. In one embodiment, the adjuvant is GLA. In another embodiment, the GLA is in the form of an oil-in-water emulsion or an aqueous form. In certain embodiments, the oil-in-water emulsion comprises squalene.

[0012] ~~In yet another embodiment of the disclosure~~Also disclosed is, a method for treating an HSV-2 infection in a subject is provided comprising administering an aforementioned composition to the subject. In a another ~~embodiment~~example, a method of generating an immune response in a subject comprising administering an aforementioned composition to the subject is provided. In still another ~~embodiment~~example, a method for immunizing a subject against HSV-2 comprising administering an aforementioned composition to the subject is provided. According to various ~~embodiments~~ example of the disclosure, an aforementioned method is provided wherein the administration route is intradermal, mucosal, intramuscular, subcutaneous, sublingual, rectal, or vaginal. In still another embodiment, an aforementioned method is provided further comprising administering a second, third or fourth composition according to any one of claims 3-8 to the subject.

[0012a] In another aspect, there is provided a use of a composition as described herein in the manufacture of a medicament for the treatment of an HSV-2 infection in a subject, wherein said medicament is to be administered to the subject.

[0012b] In another aspect, there is provided a use of a composition as described herein in the manufacture of a medicament for generating an immune response in a subject, wherein said medicament is to be administered to the subject.

[0012c] In another aspect, there is provided a use of a composition as described herein in the manufacture of a medicament for immunizing a subject against HSV-2, wherein said medicament is to be administered to the subject.

[0013] The ~~claimed invention~~present disclosure is directed to compositions and methods useful in preventing or treating HSV-2 (herpes simplex virus 2) infections in subjects, preferably humans, in one ~~embodiment~~ example the human is female, while in another ~~embodiment~~ example the human is male. The compositions comprise (i) an envelope glycoprotein of HSV-2 or an immunogenic fragment of the HSV-2 envelope glycoprotein, (ii) an HSV-2 structural protein or immunogenic fragment of the HSV-2 structural protein, wherein the structural protein is not one of the envelope glycoproteins, (iii) an agent that activates innate immunity in a subject and (iv) a pharmaceutically acceptable carrier. In certain ~~embodiments~~example, the envelope glycoprotein is gD2 and the composition has either gD2 or in an alternative ~~embodiment~~example, an immunogenic fragment derived from gD2. In

some embodiments, the structural protein is one or more of UL47, ICP0, ICP4, ICP47, UL5, UL8, UL15, UL19, UL25, UL30, UL32, UL46, UL39 (ICP10), UL7, UL40, UL54 and UL26 and if immunogenic fragments are present, they are derived from UL47, ICP0, ICP4, ICP47, UL5, UL8, UL15, UL19, UL25, UL30, UL32, UL46, UL39 (ICP10), UL7, UL40, UL54 and/or UL26. It is understood that the exact sequence of a protein may vary from one herpesvirus to another, and thus all references to an HSV-2 protein encompasses any such protein obtainable from any naturally occurring HSV-2. In other embodiments, both UL19 and UL25, or fragments from UL19 (e.g. SEQ ID NO. 12, a type of Upper Domain Fragment) and UL25, or a mixture of whole protein and fragments are present, e.g. a mixture of full length UL25 and a fragment of UL19, e.g., SEQ ID NO. 12, optionally with UL47 or a fragment thereof. At times, the agent that activates innate immunity is an adjuvant. In particular the adjuvant can be GLA or another MALA adjuvant. In one ~~embodiment~~ example the immunogenic, pharmaceutical composition comprises gD2, GLA or another MALA adjuvant, and two or three antigens selected from full length or fragments of UL25, UL19, and UL47, and a pharmaceutically acceptable carrier. In related ~~embodiments~~example, the immunogenic, pharmaceutical composition comprises a MALA adjuvant, preferably GLA having the structural formula of Figure 1, gD2, UL25, UL19 Upper Domain Fragment, and a pharmaceutically acceptable carrier; optionally such a composition further comprises one or more additional HSV-2 structural proteins, or fragments thereof.

[0014] In some ~~embodiments~~examples, the compositions comprise an antigenic portion of an envelope glycoprotein of HSV-2 and a pharmaceutically acceptable carrier. The terms 'immunogenic fragment" and "immunological fragment" and "antigenic portion" are used interchangeably herein to designate fragments or portions of proteins that elicit an antibody response or a cellular cytotoxic response that retains specificity for (cross-reactivity with) the full length protein. In certain embodiments, the antigenic portion binds to neutralizing antibodies. In certain ~~embodiments~~examples, the antigenic portion is from gD2 or gB2, and in other ~~embodiments~~examples, the antigenic portion, whether from gD2, gB2 or another envelope glycoprotein, comprises at least part and optionally all of the leader sequence. In any of the ~~embodiments~~examples, the antigenic portion comprises two or more linear epitopes or comprises two or more discontinuous epitopes from the envelope glycoprotein. In any of the ~~embodiments~~examples, the composition further comprises an agent

that activates innate immunity. The agent may be an adjuvant, such as GLA as disclosed in, for example, US Publication No. 2009/0181078.

[0015] The methods can be used to treat an HSV-2 infection or to generate an immune response, which may prevent or ameliorate an HSV-2 infection. Suitable subjects for the methods include those who are seropositive for HSV-2 as well as those who are seronegative for HSV-2. In the methods, one of the compositions described herein is administered to a subject.

[0016] Some exemplary statements of the present ~~invention~~ disclosure are set forth as follows, using the designation (xy) where each of x and y denote a letter, the designation denoting an ~~embodiment~~example, or group of ~~embodiments~~ examples when more than one (xy) is identified within an ~~embodiment~~examples. (AA) An immunogenic, pharmaceutical composition comprising (i) an envelope glycoprotein of HSV-2, or an immunological fragment thereof; (ii) a structural protein of HSV-2 other than an envelope glycoprotein of HSV-2, or an immunological fragment thereof; (iii) an agent that activates innate immunity; and (iv) a pharmaceutically acceptable carrier. (AB) Composition (AA) wherein the envelope glycoprotein of HSV-2 is gD2, and the composition comprises gD2. (AC) Composition (AA) wherein the composition comprises an immunological fragment of gD2. (AD) A composition of any one or more of (AA), (AB) and (AC), wherein the structural protein of HSV-2 is one or more proteins selected from the group consisting of UL47, ICP0, UL25, UL46, UL39, UL7, and UL26. (AE) Composition (AA) wherein the structural protein of HSV-2 is UL19. (AF) The composition of (AB) wherein the structural protein of HSV-2 is UL19. (AG) Composition (AA) wherein the structural protein of HSV-2 is an immunological fragment of UL19, e.g., SEQ ID NO. 12. (AH) Composition (AB) wherein the structural protein of HSV-2 is an immunological fragment thereof UL47. (AI) Composition (AA) wherein the structural protein of HSV-2 is UL25. (AJ) Composition (AB) wherein the structural protein of HSV-2 is UL25. (AK) Composition (AA) wherein the structural protein of HSV-2 is an immunological fragment of UL25. (AL) Composition (AB) wherein the structural protein of HSV-2 is ICP0. (AM) Composition (AA) wherein the structural protein of HSV-2 is UL47. (AN) Composition (AB) wherein the structural protein of HSV-2 is a fragment of UL47. (AO) Composition (AA) wherein the structural protein of HSV-2 other than an

adjuvant is GLA or another MALA adjuvant, and each and every one of the options in (BG) is independently selected as a distinct embodiment of the present invention. (BI) Composition (AA) comprising gD2; UL25; UL19; GLA or another MALA adjuvant; and a pharmaceutically acceptable carrier. (BJ) Composition (AA) comprising gD2, UL25 and an immunological fragment of UL19. (BK) Composition (AA) comprising gD2, UL19, and an immunological fragment of UL25. (BL) A composition of any one or more of (BI), (BJ) and (BK) further comprising UL47. (BM) A composition of any one or more of (BI), (BJ) and (BK) further comprising an immunological fragment of UL47. (BN) A method for treating an HSV-2 infection in a subject, comprising administering the composition of any one or more of (AA), (AB), (AC), (AD), (AE), (AF), (AG), (AH), (AI), (AJ), (AK), (AL), (AM), (AN), (AO), (AP), (AQ), (AR), (AS), (AT), (AU), (AV), (AW), (AX), (AY), (AZ), (BA), (BB), (BC), (BD), (BE), (BF), (BG), (BH), (BI), (BJ), (BK), (BL), and (BM) to the subject. (BO) A method for generating an immune response to HSV-2 in a subject, comprising administering the composition of any one or more of (AA), (AB), (AC), (AD), (AE), (AF), (AG), (AH), (AI), (AJ), (AK), (AL), (AM), (AN), (AO), (AP), (AQ), (AR), (AS), (AT), (AU), (AV), (AW), (AX), (AY), (AZ), (BA), (BB), (BC), (BD), (BE), (BF), (BG), (BH), (BI), (BJ), (BK), (BL), (BM), and (BN) to the subject. (BQ) Method (BO) wherein the subject is seropositive for HSV-2 and seropositive for HSV-1. (BR) Method (BO) wherein the subject is seropositive for HSV-2 and seronegative for HSV-1.

[0017] ~~In one embodiment there is provided~~Also disclosed is a composition comprising an envelope glycoprotein of HSV-2 or an immunological fragment thereof; two structural proteins of HSV-2 other than an envelope glycoprotein of HSV-2, or an immunological fragment thereof; an agent that activates innate immunity; and a pharmaceutically acceptable carrier. Exemplary is a composition that comprises gD2, UL25, and SEQ ID NO. 12 (a fragment of UL19) and a monophosphoryl lipid A (MALA) adjuvant, e.g., GLA. In addition to gD2-specific antibody responses, vaccination with this composition may elicit robust HSV-2 antigen-specific CD4 and CD8 effector and memory T cells that respond to subsequent infection with live virus. Notably, prophylactic immunization with this composition may largely or completely protect against lethal intravaginal HSV-2 infection in C57BL/6 mice, with sterilizing immunity in both the genital mucosa and dorsal root ganglia. This composition may expand both

(d) an immunogenic fragment of (a) or (b); and

(e) a chimeric fusion of (a), (b) or (c);

(ii) optionally, an agent that activates innate immunity; and

(iii) a pharmaceutically acceptable carrier.

4. The composition of claim 3 which further comprises UL25 or an immunogenic fragment thereof.

5. The composition of any one of claims 3 and 4 which further comprises gD2 or an immunogenic fragment thereof.

6. The composition of any of claims 3-5 wherein the agent is an adjuvant.

7. The composition of claim 6 wherein the adjuvant is GLA.

8. The composition of claim 7 wherein the GLA is in the form of an oil-in-water emulsion or is in an aqueous form.

9. The composition of claim 8 wherein the oil-in-water emulsion comprises squalene.

10. ~~A method for treating an HSV-2 infection in a subject comprising administering the~~ Use of a composition of any one of claims 3-9 in the manufacture of a medicament for the treatment of an HSV-2 infection in a subject~~to the subject~~, wherein said medicament is to be administered to the subject.

11. ~~A method of generating an immune response in a subject comprising administering~~ Use of a~~the~~ composition of any one of claims 3-9 ~~to the subject~~in the manufacture of a medicament for generating an immune response in a subject, wherein said medicament is to be administered to the subject.

12. ~~A method for immunizing a subject against HSV-2 comprising administering~~ Use of ~~the~~ a composition of any one of claims 3-9 in the manufacture of a medicament for immunizing a subject against HSV-2~~to the subject~~, wherein said medicament is to be administered to the subject.

13. The ~~method~~ use of any one of claims 9-12 wherein the administration route is intradermal, mucosal, intramuscular, subcutaneous, sublingual, rectal, or vaginal.

14. The ~~method~~ use of any one of claims 9-13 further comprising ~~administering~~ administration of a second, third or fourth composition according to any one of claims 3-9 to the subject.