(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
05 April 2018 (05.04.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/064232 A1

(51) International Patent Classification:
C07K 14/035 (2006.01) *A61K 39/245* (2006.01)
G01N 33/569 (2006.01) *C12N 7/04* (2006.01)
A61K 38/00 (2006.01)

(21) International Application Number:
PCT/US2017/053835

(22) International Filing Date:
27 September 2017 (27.09.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/401,148 28 September 2016 (28.09.2016) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

(54) Title: METHODS AND COMPOSITIONS FOR TREATING HERPES

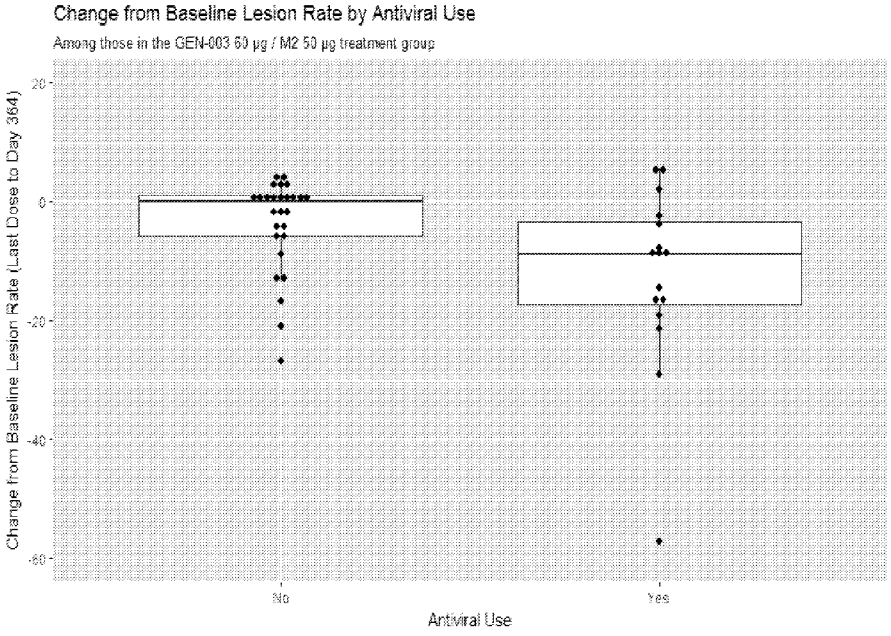

FIGURE 2

(57) Abstract: The present disclosure provides, *inter alia*, certain combinations of immunogenic compositions (e.g., vaccines) against HSV-2 and antiviral therapy. The vaccines can be used therapeutically and/or prophylactically.

[Continued on next page]

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Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

METHODS AND COMPOSITIONS FOR TREATING HERPES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims benefit under 35 U.S.C. 119(e) of U.S. Provisional Application No. 62/401,148 filed September 28, 2016, the contents of which are incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on September 25, 2017, is named 2007781-0179_SL.txt and is 322,611 bytes in size.

BACKGROUND

[0003] Herpes simplex viruses (HSVs) are a main cause of genital ulcers worldwide, (see, the world wide web at the hypertext protocol transfer address of "who.int/bulletin/volumes/86/10/07-046128/en/index.html"). Of the 2 types of HSV, type 2 (HSV-2) is a more common cause of genital herpes and one of the most common sexually transmitted diseases with nearly 500 million people affected worldwide. Evidence of infection, by serologic studies, is present in 1 out of every 6 people aged 14 to 49 in the United States (see, the world wide web at the hypertext protocol transfer address of "niaid.nih.gov/topics/genitalherpes/Pages/default.aspx"; Centers for Disease Control, MMWR Morb Mortal Wkly Rep. (2010) 59:456–9). Women are more commonly infected than men, with 1 out of every 5 women in the US having evidence of infection. Certain groups, such as people with human immunodeficiency virus (HIV) and commercial sex workers, have high rates of infection ranging from 60% to 95%, (Kimberlin & Rouse, New Engl J Med. (2004) 350:1970–7; Gupta et al., Lancet. (2007) 370:2127–37).

[0004] To date, there are no known curative treatments or approved therapeutic vaccines for HSV-2 infection. Current therapy is directed at reducing the duration of primary disease or reducing the duration or frequency of secondary outbreaks. Accordingly, there remains a need for effective therapies to treat HSV-2 infection.

SUMMARY

[0005] The invention is based, at least in part, on the discovery that administration of an immunogenic composition and an antiviral therapy is effective therapy for herpes, e.g., herpes infection. Accordingly, in one aspect, the disclosure features a method of treating herpes infection. In some embodiments, the method comprises administering an antiviral therapy (e.g., an antiviral therapy described herein, e.g., famciclovir, valacyclovir, acyclovir or a combination thereof) to a subject. In some embodiments, the subject is receiving and/or has received an immunogenic composition (e.g., a vaccine composition described herein).

[0006] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) is improved in the subject, e.g., over a time period, relative to a subject receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject receiving only the antiviral therapy. In some embodiments, efficacy of the antiviral therapy is improved in the subject, e.g., over a time period, relative to a subject receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition) or only the antiviral therapy. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and efficacy of the antiviral therapy is improved in the subject, e.g., over a time period, relative to a subject receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition) or only the antiviral therapy.

[0007] In some embodiments, the immunogenic composition (e.g., vaccine composition) comprises an HSV-2 gD2 polypeptide (or immunogenic fragment) and/or an HSV-2 ICP4 polypeptide (or immunogenic fragment). In some embodiments, the gD2 polypeptide has an

internal deletion of all or part of the transmembrane domain. In some embodiments, the ICP4 polypeptide comprises at least 8 contiguous amino acids of an ICP4 polypeptide. In some embodiments, the immunogenic composition comprises an HSV-2 gD2 polypeptide comprising (i) an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:4; and (ii) an HSV-2 ICP4 polypeptide comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:2. In some embodiments, the immunogenic composition comprises an adjuvant, e.g., one or more purified fractions of *Quillaja saponins*.

[0008] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, an increase in time to first herpes recurrence, an increase in time to next herpes recurrence, a decrease in genital herpes lesion rate, a decrease in genital herpes lesion frequency, a decrease in genital herpes lesion duration, a decrease in rate of genital herpes outbreaks, a decrease in duration of genital herpes outbreaks, a decrease in anogenital HSV shedding rate, a decrease in anogenital HSV shedding magnitude, a decrease or no increase in antiviral dose, a decrease in one or more herpes signs or symptoms, an increase in health-related quality of life, a decrease in time to lesion healing, a decrease in time to cessation of pain, a decrease in time to cessation of viral shedding, a decrease in herpes recurrence rate, a decrease in rate of symptomatic acquisition of herpes in a susceptible partner, an increase in humoral response, and an increase in cellular response.

[0009] In some embodiments, the method further comprises administering the antiviral therapy (e.g., an antiviral therapy described herein, e.g., famciclovir, valacyclovir, acyclovir or a combination thereof) to a population of subjects receiving and/or who have received an immunogenic composition (e.g., a vaccine composition described herein). In some

embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy.

[0010] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, an increase in time to first herpes recurrence, an increase in time to next herpes recurrence, a decrease in genital herpes lesion rate, a decrease in genital herpes lesion frequency, a decrease in genital herpes lesion duration, a decrease in rate of genital herpes outbreaks, a decrease in duration of genital herpes outbreaks, a decrease in anogenital HSV shedding rate, a decrease in anogenital HSV shedding magnitude, a decrease or no increase in antiviral dose, a decrease in one or more herpes signs or symptoms, an increase in health-related quality of life, a decrease in time to lesion healing, a decrease in time to cessation of pain, a decrease in time to cessation of viral shedding, a decrease in herpes recurrence rate, a decrease in rate of symptomatic acquisition of herpes in a susceptible partner, an increase in humoral response, and an increase in cellular response.

[0011] In another aspect, the disclosure features a method of treating herpes infection. In some embodiments, the method comprises administering an antiviral therapy (e.g., an antiviral therapy described herein, e.g., famciclovir, valacyclovir, acyclovir or a combination thereof) to a population of subjects. In some embodiments, the population of subjects is receiving and/or has received an immunogenic composition (e.g., a vaccine composition described herein).

[0012] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy.

[0013] In some embodiments, the immunogenic composition (e.g., vaccine composition) comprises an HSV-2 gD2 polypeptide (or immunogenic fragment) and/or an HSV-2 ICP4 polypeptide (or immunogenic fragment). In some embodiments, the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain. In some embodiments, the ICP4 polypeptide comprises at least 8 contiguous amino acids of an ICP4 polypeptide. In some embodiments, the immunogenic composition comprises an HSV-2 gD2 polypeptide comprising

(i) an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:4; and (ii) an HSV-2 ICP4 polypeptide comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:2. In some embodiments, the immunogenic composition comprises an adjuvant, e.g., one or more purified fractions of *Quillaja saponins*.

[0014] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, an increase in time to first herpes recurrence, an increase in time to next herpes recurrence, a decrease in genital herpes lesion rate, a decrease in genital herpes lesion frequency, a decrease in genital herpes lesion duration, a decrease in rate of genital herpes outbreaks, a decrease in duration of genital herpes outbreaks, a decrease in anogenital HSV shedding rate, a decrease in anogenital HSV shedding magnitude, a decrease or no increase in antiviral dose, a decrease in one or more herpes signs or symptoms, an increase in health-related quality of life, a decrease in time to lesion healing, a decrease in time to cessation of pain, a decrease in time to cessation of viral shedding, a decrease in herpes recurrence rate, a decrease in rate of symptomatic acquisition of herpes in a susceptible partner, an increase in humoral response, and an increase in cellular response.

[0015] In another aspect, the disclosure features a method of treating herpes infection. In some embodiments, the method comprises administering to a subject an immunogenic composition (e.g., a vaccine composition described herein). In some embodiments, the subject is receiving and/or has received an antiviral therapy (e.g., an antiviral therapy described herein, e.g., famciclovir, valacyclovir, acyclovir or a combination thereof).

[0016] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) is improved in the subject, e.g., over a time period, relative to a subject receiving

neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject receiving only the antiviral therapy. In some embodiments, efficacy of the antiviral therapy is improved in the subject, e.g., over a time period, relative to a subject receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition) or only the antiviral therapy. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and efficacy of the antiviral therapy is improved in the subject, e.g., over a time period, relative to a subject receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition) or only the antiviral therapy.

[0017] In some embodiments, the immunogenic composition (e.g., vaccine composition) comprises an HSV-2 gD2 polypeptide (or immunogenic fragment) and/or an HSV-2 ICP4 polypeptide (or immunogenic fragment). In some embodiments, the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain. In some embodiments, the ICP4 polypeptide comprises at least 8 contiguous amino acids of an ICP4 polypeptide. In some embodiments, the immunogenic composition comprises an HSV-2 gD2 polypeptide comprising (i) an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:4; and (ii) an HSV-2 ICP4 polypeptide comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:2. In some embodiments, the immunogenic composition comprises an adjuvant, e.g., one or more purified fractions of *Quillaja saponins*.

[0018] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and/or the antiviral therapy is measured or indicated by one or more of: a genital

herpes recurrence-free period, an increase in time to first herpes recurrence, an increase in time to next herpes recurrence, a decrease in genital herpes lesion rate, a decrease in genital herpes lesion frequency, a decrease in genital herpes lesion duration, a decrease in rate of genital herpes outbreaks, a decrease in duration of genital herpes outbreaks, a decrease in anogenital HSV shedding rate, a decrease in anogenital HSV shedding magnitude, a decrease or no increase in antiviral dose, a decrease in one or more herpes signs or symptoms, an increase in health-related quality of life, a decrease in time to lesion healing, a decrease in time to cessation of pain, a decrease in time to cessation of viral shedding, a decrease in herpes recurrence rate, a decrease in rate of symptomatic acquisition of herpes in a susceptible partner, an increase in humoral response, and an increase in cellular response.

[0019] In some embodiments, the method further comprises administering the immunogenic composition (e.g., vaccine composition) to a population of subjects receiving and/or who have received antiviral therapy (e.g., an antiviral therapy described herein, e.g., famciclovir, valacyclovir, acyclovir or a combination thereof). In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving

only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy.

[0020] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, an increase in time to first herpes recurrence, an increase in time to next herpes recurrence, a decrease in genital herpes lesion rate, a decrease in genital herpes lesion frequency, a decrease in genital herpes lesion duration, a decrease in rate of genital herpes outbreaks, a decrease in duration of genital herpes outbreaks, a decrease in anogenital HSV shedding rate, a decrease in anogenital HSV shedding magnitude, a decrease or no increase in antiviral dose, a decrease in one or more herpes signs or symptoms, an increase in health-related quality of life, a decrease in time to lesion healing, a decrease in time to cessation of pain, a decrease in time to cessation of viral shedding, a decrease in herpes recurrence rate, a decrease in rate of symptomatic acquisition of herpes in a susceptible partner, an increase in humoral response, and an increase in cellular response.

[0021] In another aspect, the disclosure features a method of treating herpes infection. In some embodiments, the method comprises administering an immunogenic composition (e.g., vaccine composition) to a population of subjects. In some embodiments, the population of subjects is receiving and/or has received antiviral therapy (e.g., an antiviral therapy described herein, e.g., famciclovir, valacyclovir, acyclovir or a combination thereof).

[0022] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g.,

vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy.

[0023] In some embodiments, the immunogenic composition (e.g., vaccine composition) comprises an HSV-2 gD2 polypeptide (or immunogenic fragment) and/or an HSV-2 ICP4 polypeptide (or immunogenic fragment). In some embodiments, the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain. In some embodiments, the ICP4 polypeptide comprises at least 8 contiguous amino acids of an ICP4 polypeptide. In some embodiments, the immunogenic composition comprises an HSV-2 gD2 polypeptide comprising (i) an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:4; and (ii) an HSV-2 ICP4 polypeptide comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:2. In some embodiments, the immunogenic composition comprises an adjuvant, e.g., one or more purified fractions of *Quillaja saponins*.

[0024] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, an increase in time to first herpes recurrence, an increase in time to next herpes recurrence, a decrease in genital herpes lesion rate, a decrease in genital herpes lesion frequency, a decrease in genital herpes lesion duration, a decrease in rate of genital herpes

outbreaks, a decrease in duration of genital herpes outbreaks, a decrease in anogenital HSV shedding rate, a decrease in anogenital HSV shedding magnitude, a decrease or no increase in antiviral dose, a decrease in one or more herpes signs or symptoms, an increase in health-related quality of life, a decrease in time to lesion healing, a decrease in time to cessation of pain, a decrease in time to cessation of viral shedding, a decrease in herpes recurrence rate, a decrease in rate of symptomatic acquisition of herpes in a susceptible partner, an increase in humoral response, and an increase in cellular response.

[0025] In another aspect, the disclosure features a method of treating herpes infection. In some embodiments, the method comprises administering to a subject (i) an antiviral therapy (e.g., an antiviral therapy described herein, e.g., famciclovir, valacyclovir, acyclovir or a combination thereof); and (ii) an immunogenic composition (e.g., a vaccine composition described herein). In some embodiments, the antiviral therapy and the immunogenic composition are administered concurrently. In some embodiments, the antiviral therapy and the immunogenic composition are administered sequentially.

[0026] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) is improved in the subject, e.g., over a time period, relative to a subject receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject receiving only the antiviral therapy. In some embodiments, efficacy of the antiviral therapy is improved in the subject, e.g., over a time period, relative to a subject receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition) or only the antiviral therapy. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and efficacy of the antiviral therapy is improved in the subject, e.g., over a time period, relative to a subject receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject receiving only the immunogenic composition (e.g., vaccine composition) or only the antiviral therapy.

[0027] In some embodiments, the immunogenic composition (e.g., vaccine composition) comprises an HSV-2 gD2 polypeptide (or immunogenic fragment) and/or an HSV-2 ICP4

polypeptide (or immunogenic fragment). In some embodiments, the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain. In some embodiments, the ICP4 polypeptide comprises at least 8 contiguous amino acids of an ICP4 polypeptide. In some embodiments, the immunogenic composition comprises an HSV-2 gD2 polypeptide comprising (i) an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:4 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:4; and (ii) an HSV-2 ICP4 polypeptide comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2, or an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO:2 and lacking 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids from the amino terminus and/or carboxyl terminus of SEQ ID NO:2. In some embodiments, the immunogenic composition comprises an adjuvant, e.g., one or more purified fractions of *Quillaja saponins*.

[0028] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, an increase in time to first herpes recurrence, an increase in time to next herpes recurrence, a decrease in genital herpes lesion rate, a decrease in genital herpes lesion frequency, a decrease in genital herpes lesion duration, a decrease in rate of genital herpes outbreaks, a decrease in duration of genital herpes outbreaks, a decrease in anogenital HSV shedding rate, a decrease in anogenital HSV shedding magnitude, a decrease or no increase in antiviral dose, a decrease in one or more herpes signs or symptoms, an increase in health-related quality of life, a decrease in time to lesion healing, a decrease in time to cessation of pain, a decrease in time to cessation of viral shedding, a decrease in herpes recurrence rate, a decrease in rate of symptomatic acquisition of herpes in a susceptible partner, an increase in humoral response, and an increase in cellular response.

[0029] In some embodiments, the method comprises administering (i) an antiviral therapy (e.g., an antiviral therapy described herein, e.g., famciclovir, valacyclovir, acyclovir or a combination thereof); and (ii) an immunogenic composition (e.g., a vaccine composition

described herein to a population of subjects. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy. In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and efficacy of the antiviral therapy is improved in the population (or a subset of the population), e.g., over a time period, relative to a subject or population of subjects receiving neither the immunogenic composition (e.g., vaccine composition) nor the antiviral therapy, relative to a subject or population of subjects receiving only the immunogenic composition (e.g., vaccine composition), or relative to a subject or population of subjects receiving only the antiviral therapy.

[0030] In some embodiments, efficacy of the immunogenic composition (e.g., vaccine composition) and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, an increase in time to first herpes recurrence, an increase in time to next herpes recurrence, a decrease in genital herpes lesion rate, a decrease in genital herpes lesion frequency, a decrease in genital herpes lesion duration, a decrease in rate of genital herpes outbreaks, a decrease in duration of genital herpes outbreaks, a decrease in anogenital HSV shedding rate, a decrease in anogenital HSV shedding magnitude, a decrease or no increase in antiviral dose, a decrease in one or more herpes signs or symptoms, an increase in health-related quality of life, a decrease in time to lesion healing, a decrease in time to cessation of pain, a decrease in time to cessation of viral shedding, a decrease in herpes recurrence rate, a decrease in

rate of symptomatic acquisition of herpes in a susceptible partner, an increase in humoral response, and an increase in cellular response.

[0031] In any of the aspects described herein, a subject or population of subjects is receiving, has received, or is administered about 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.1 g, 1.2 g, 1.3 g, 1.4 g, 1.5 g, 100-300 mg, 200-400 mg, 300-500 mg, 400-600 mg, 500-700 mg, 600-800 mg, 700-900 mg, 800-1000 mg, or more, of antiviral therapy per dose.

[0032] In any of the aspects described herein, a subject or population of subjects is receiving, has received, or is administered an immunogenic composition described herein comprising about 10 μg, 20 μg, 30 μg, 60 μg, or 100 μg of each of a gD2 polypeptide described herein and an ICP4 polypeptide described herein and/or about 25 μg, 50 μg or 75 μg of adjuvant described herein.

[0033] In any of the aspects described herein, efficacy of the immunogenic composition and/or antiviral therapy is assessed at, e.g., at least 3 months, 6 months, 12 months, 18 months, 24 months, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, or 10 years after administration of the immunogenic composition and/or antiviral therapy.

[0034] In any of the aspects described herein, the subject or population of subjects: have not received and/or are not receiving therapy comprising tenofovir, lysine, a supplement or medication, other than valacyclovir, e.g., a therapy known to or purported to affect herpes outbreak frequency or intensity; do not have a history of ocular herpes infection, herpes-related erythema multiforme, herpes meningitis or herpes encephalitis; do not have active genital HSV-2 lesions; are not immunocompromised; are not receiving systemic immunosuppressive medication; do not have an autoimmune disease; have not previously had an autoimmune disease; do not have HIV, hepatitis B or hepatitis C; do not have history of hypersensitivity to any component of the vaccine formulation; do not have a clinically significant laboratory abnormality except for (i) creatinine kinase in subjects with an identified exercise regimen and hepatic and renal enzyme levels within normal limits or (ii) isolated Grade 2 unconjugated bilirubin in fasting subjects with a history of Gilbert's syndrome; have not received any other

vaccine containing an HSV-2 antigen; have not received an investigational product within 30 days prior to the first dose of the vaccine formulation; have not received a blood product within 90 days prior to the first dose of the vaccine formulation; have not received a live vaccine within 28 days prior to the first dose of the vaccine formulation; have not received any other vaccine within 14 days prior to the first dose of the vaccine formulation; do not receive any other vaccine from the first dose until 28 days after the third dose; are not pregnant or nursing; or any combination thereof.

[0035] In any of the aspects described herein, the subject or population of subjects: is male, female or non-pregnant female; is at least 18 years old and less than 51 years old, is at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, or 60 years old, are 51 years or older; are receiving antiviral therapy; have a history of at least one genital herpes outbreak while on antiviral therapy within about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months of treatment; have a history of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more outbreaks of genital herpes within one year if not receiving antiviral therapy; have been diagnosed with genital herpes infection for greater than 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or more months; use contraception for about 1, 7, 14, 21, 28, 35, or 42 days before and/or about 15, 30, 45, 60, 75, 90, 105, or 120 days after treatment with the immunogenic composition; or any combination thereof.

[0036] In any of the aspects described herein, the immunogenic composition treats infection by HSV-1, HSV-2, or HSV-1 and HSV-2 in the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] The Figures described below, that together make up the Drawing, are for illustration purposes only, not for limitation.

[0038] **Figures 1A-1D** depict exemplary Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

[0039] **Figure 2** depicts exemplary data showing the change from baseline genital lesion rates for those in the 60 μg GEN-003 + 50 μg Matrix-M2 treatment group who never took antiviral therapy during the study period and those who took antiviral therapy at least once.

[0040] **Figure 3** depicts exemplary data comparing the genital lesion rate of subjects in the 60 μg GEN-003 + 50 μg Matrix-M2 dose group who took antiviral therapy at least once during the study period to the genital lesion rate of those in the placebo group who took antiviral therapy at least once during the study period.

[0041] **Figure 4** depicts exemplary data showing an association between days on anti-viral therapy and change from baseline genital lesion rate among subjects receiving 60 μg GEN-003 + 50 μg Matrix-M2.

DEFINITIONS

[0042] In this application, unless otherwise clear from context, (i) the term "a" may be understood to mean "at least one"; (ii) the term "or" may be understood to mean "and/or"; (iii) the terms "comprising" and "including" may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; and (iv) the terms "about" and "approximately" may be understood to permit standard variation as would be understood by those of ordinary skill in the art; and (v) where ranges are provided, endpoints are included.

[0043] ***Administration:*** As used herein, the term "administration" typically refers to the administration of a composition to a subject or system. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments, administration may be ocular, oral, parenteral, topical, etc.. In some particular embodiments, administration may be bronchial (e.g., by bronchial instillation), buccal, dermal (which may be or comprise, for example, one or more of topical to the dermis, intradermal, interdermal, transdermal, etc), enteral, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, within a specific organ (e. g.

intrahepatic), mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (e.g., by intratracheal instillation), vaginal, vitreal, etc. In some embodiments, administration may involve dosing that is intermittent (e.g., a plurality of doses separated in time) and/or periodic (e.g., individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (e.g., perfusion) for at least a selected period of time.

[0044] ***Agent*** : In general, the term "agent", as used herein, may be used to refer to a compound or entity of any chemical class including, for example, a polypeptide, nucleic acid, saccharide, lipid, small molecule, metal, or combination or complex thereof. In appropriate circumstances, as will be clear from context to those skilled in the art, the term may be utilized to refer to an entity that is or comprises a cell or organism, or a fraction, extract, or component thereof. Alternatively or additionally, as context will make clear, the term may be used to refer to a natural product in that it is found in and/or is obtained from nature. In some instances, again as will be clear from context, the term may be used to refer to one or more entities that is man-made in that it is designed, engineered, and/or produced through action of the hand of man and/or is not found in nature. In some embodiments, an agent may be utilized in isolated or pure form; in some embodiments, an agent may be utilized in crude form. In some embodiments, potential agents may be provided as collections or libraries, for example that may be screened to identify or characterize active agents within them. In some cases, the term "agent" may refer to a compound or entity that is or comprises a polymer; in some cases, the term may refer to a compound or entity that comprises one or more polymeric moieties. In some embodiments, the term "agent" may refer to a compound or entity that is not a polymer and/or is substantially free of any polymer and/or of one or more particular polymeric moieties. In some embodiments, the term may refer to a compound or entity that lacks or is substantially free of any polymeric moiety.

[0045] ***Amelioration:*** as used herein, refers to the prevention, reduction or palliation of a state, or improvement of the state of a subject. Amelioration includes, but does not require complete recovery or complete prevention of a disease, disorder or condition (e.g., radiation injury).

[0046] ***Inhibitor:*** As used herein, the term "inhibitor" refers to an agent, condition, or event whose presence, level, degree, type, or form correlates with decreased level or activity of another agent (i.e., the inhibited agent, or target). In general, an inhibitor may be or include an agent of any chemical class including, for example, small molecules, polypeptides, nucleic acids, carbohydrates, lipids, metals, and/or any other entity, condition or event that shows the relevant inhibitory activity. In some embodiments, an inhibitor may be direct (in which case it exerts its influence directly upon its target, for example by binding to the target); in some embodiments, an inhibitor may be indirect (in which case it exerts its influence by interacting with and/or otherwise altering a regulator of the target, so that level and/or activity of the target is reduced).

[0047] ***Antiviral agent***: As used herein, the term "antiviral agent" refers to a class of medication used specifically for treating viral infections by inhibiting, deactivating, or destroying virus particles. In general, an antiviral agent may be or comprises a compound of any chemical class (e.g., a small molecule, metal, nucleic acid, polypeptide, lipid and/or carbohydrate). In some embodiments, an antiviral agent is or comprises an antibody or antibody mimic. In some embodiments, an antiviral agent is or comprises a nucleic acid agent (e.g., an antisense oligonucleotide, a siRNA, a shRNA, etc) or mimic thereof. In some embodiments, an antiviral agent is or comprises a small molecule. In some embodiments, an antiviral agent is or comprises a naturally-occurring compound (e.g., small molecule). In some embodiments, an antiviral agent has a chemical structure that is generated and/or modified by the hand of man.

[0048] ***Approximately:*** As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0049] ***Associated with:*** Two events or entities are "associated" with one another, as that term is used herein, if the presence, level and/or form of one is correlated with that of the other. For example, a particular entity (e.g., polypeptide, genetic signature, metabolite, microbe, etc) is

considered to be associated with a particular disease, disorder, or condition, if its presence, level and/or form correlates with incidence of and/or susceptibility to the disease, disorder, or condition (e.g., across a relevant population). In some embodiments, two or more entities are physically "associated" with one another if they interact, directly or indirectly, so that they are and/or remain in physical proximity with one another. In some embodiments, two or more entities that are physically associated with one another are covalently linked to one another; in some embodiments, two or more entities that are physically associated with one another are not covalently linked to one another but are non-covalently associated, for example by means of hydrogen bonds, van der Waals interaction, hydrophobic interactions, magnetism, and combinations thereof.

[0050] ***Biologically active:*** as used herein, refers to an observable biological effect or result achieved by an agent or entity of interest. For example, in some embodiments, a specific binding interaction is a biological activity. In some embodiments, modulation (e.g., induction, enhancement, or inhibition) of a biological pathway or event is a biological activity. In some embodiments, presence or extent of a biological activity is assessed through detection of a direct or indirect product produced by a biological pathway or event of interest.

[0051] ***Combination therapy:*** As used herein, the term "combination therapy" refers to those situations in which a subject is simultaneously exposed to two or more therapeutic regimens (e.g., two or more therapeutic agents). In some embodiments, the two or more regimens may be administered simultaneously; in some embodiments, such regimens may be administered sequentially (e.g., all "doses" of a first regimen are administered prior to administration of any doses of a second regimen); in some embodiments, such agents are administered in overlapping dosing regimens. In some embodiments, "administration" of combination therapy may involve administration of one or more agents or modalities to a subject receiving the other agents or modalities in the combination. For clarity, combination therapy does not require that individual agents be administered together in a single composition (or even necessarily at the same time), although in some embodiments, two or more agents, or active moieties thereof, may be administered together in a combination composition, or even in a combination compound (e.g., as part of a single chemical complex or covalent entity).

[0052] ***Comparable***: As used herein, the term "comparable" refers to two or more agents, entities, situations, sets of conditions, etc., that may not be identical to one another but that are sufficiently similar to permit comparison therebetween so that one skilled in the art will appreciate that conclusions may reasonably be drawn based on differences or similarities observed. In some embodiments, comparable sets of conditions, circumstances, individuals, or populations are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will understand, in context, what degree of identity is required in any given circumstance for two or more such agents, entities, situations, sets of conditions, etc. to be considered comparable. For example, those of ordinary skill in the art will appreciate that sets of circumstances, individuals, or populations are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under or with different sets of circumstances, individuals, or populations are caused by or indicative of the variation in those features that are varied.

[0053] ***Corresponding to***: As used herein designates the position/identity of a structural element in a compound or composition through comparison with an appropriate reference compound or composition. For example, in some embodiments, a monomeric residue in a polymer (e.g., an amino acid residue in a polypeptide or a nucleic acid residue in a polynucleotide) may be identified as "corresponding to" a residue in an appropriate reference polymer.. For example, those of ordinary skill will appreciate that, for purposes of simplicity, residues in a polypeptide are often designated using a canonical numbering system based on a reference related polypeptide, so that an amino acid "*corresponding to*" a residue at position 190, for example, need not actually be the 190th amino acid in a particular amino acid chain but rather corresponds to the residue found at 190 in the reference polypeptide; those of ordinary skill in the art readily appreciate how to identify "*corresponding*" amino acids.

[0054] ***Determine:*** Many methodologies described herein include a step of "determining". Those of ordinary skill in the art, reading the present specification, will appreciate that such "determining" can utilize or be accomplished through use of any of a variety of techniques available to those skilled in the art, including for example specific techniques

explicitly referred to herein. In some embodiments, determining involves manipulation of a physical sample. In some embodiments, determining involves consideration and/or manipulation of data or information, for example utilizing a computer or other processing unit adapted to perform a relevant analysis. In some embodiments, determining involves receiving relevant information and/or materials from a source. In some embodiments, determining involves comparing one or more features of a sample or entity to a comparable reference.

[0055] ***Diagnostic information:*** As used herein, "diagnostic information" or "information for use in diagnosis" is information that is useful in determining whether a patient has a disease, disorder or condition and/or in classifying a disease, disorder or condition into a phenotypic category or any category having significance with regard to prognosis of a disease, disorder or condition, or likely response to treatment (either treatment in general or any particular treatment) of a disease, disorder or condition. Similarly, "diagnosis" refers to providing any type of diagnostic information, including, but not limited to, whether a subject is likely to have or develop a disease, disorder or condition, state, staging or characteristic of a disease, disorder or condition as manifested in the subject, information related to the nature or classification of a tumor, information related to prognosis and/or information useful in selecting an appropriate treatment. Selection of treatment may include the choice of a particular therapeutic agent or other treatment modalitiy such as surgery, radiation, etc., a choice about whether to withhold or deliver therapy, a choice relating to dosing regimen (e.g., frequency or level of one or more doses of a particular therapeutic agent or combination of therapeutic agents), etc.

[0056] ***Dosage form* or *unit dosage form:*** Those skilled in the art will appreciate that the term "dosage form" may be used to refer to a physically discrete unit of an active agent (e.g., a therapeutic or diagnostic agent) for administration to a subject. Typically, each such unit contains a predetermined quantity of active agent. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen). Those of ordinary skill in the art appreciate that the total amount of a therapeutic composition or agent administered

to a particular subject is determined by one or more attending physicians and may involve administration of multiple dosage forms.

[0057] ***Dosing regimen:*** Those skilled in the art will appreciate that the term "dosing regimen" may be used to refer o a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which is separated in time from other doses. In some embodiments, individual doses are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

[0058] ***Fragment:*** A "fragment" of a material or entity as described herein has a structure that includes a discrete portion of the whole, but lacks one or more moieties found in the whole. In some embodiments, a fragment consists of such a discrete portion. In some embodiments, a fragment consists of or comprises a characteristic structural element or moiety found in the whole. In some embodiments, a polymer fragment comprises or consists of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500 or more monomeric units (e.g., residues) as found in the whole polymer. In some embodiments, a polymer fragment comprises or consists of at least about 5%, 10%, 15%, 20%, 25%, 30%, 25%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more of the monomeric units (e.g.,

residues) found in the whole polymer. The whole material or entity may in some embodiments be referred to as the "parent" of the whole.

[0059] ***Functional:*** As used herein, a "functional" biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized. A biological molecule may have two functions (i.e., bifunctional) or many functions (i.e., multifunctional).

[0060] ***Identity***: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, *e.g.*, between nucleic acid molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "substantially identical" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical. Calculation of the percent identity of two nucleic acid or polypeptide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or substantially 100% of the length of a reference sequence. The nucleotides at corresponding positions are then compared. When a position in the first sequence is occupied by the same residue (e.g., nucleotide or amino acid) as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4: 11-17), which has been incorporated into the ALIGN program (version 2.0). In some exemplary embodiments, nucleic acid sequence comparisons made with the ALIGN program use a PAM120 weight residue table, a gap length penalty of 12

and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix.

[0061] ***Improve,*" "*increase*" or "*reduce:*** As used herein or grammatical equivalents thereof, indicate values that are relative to a baseline measurement, such as a measurement in the same individual prior to initiation of a treatment described herein, or a measurement in a control individual (or multiple control individuals) in the absence of the treatment described herein. In some embodiments, a "*control individual*" is an individual afflicted with the same form of disease or injury as an individual being treated.

[0062] ***Isolated:*** as used herein, refers to a substance and/or entity that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature and/or in an experimental setting), and/or (2) designed, produced, prepared, and/or manufactured by the hand of man. Isolated substances and/or entities may be separated from about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% of the other components with which they were initially associated. In some embodiments, isolated agents are about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "*pure*" if it is substantially free of other components. In some embodiments, as will be understood by those skilled in the art, a substance may still be considered "*isolated*" or even "*pure*", after having been combined with certain other components such as, for example, one or more carriers or excipients (e.g., buffer, solvent, water, etc.); in such embodiments, percent isolation or purity of the substance is calculated without including such carriers or excipients. To give but one example, in some embodiments, a biological polymer such as a polypeptide or polynucleotide that occurs in nature is considered to be "*isolated*" when, a) by virtue of its origin or source of derivation is not associated with some or all of the components that accompany it in its native state in nature; b) it is substantially free of other polypeptides or nucleic acids of the same species from the species that produces it in nature; c) is expressed by or is otherwise in

association with components from a cell or other expression system that is not of the species that produces it in nature. Thus, for instance, in some embodiments, a polypeptide that is chemically synthesized or is synthesized in a cellular system different from that which produces it in nature is considered to be an "*isolated*" polypeptide. Alternatively or additionally, in some embodiments, a polypeptide that has been subjected to one or more purification techniques may be considered to be an "*isolated*" polypeptide to the extent that it has been separated from other components a) with which it is associated in nature; and/or b) with which it was associated when initially produced.

[0063] ***Patient:*** As used herein, the term "patient" refers to any organism to which a provided composition is or may be administered, e.g., for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and/or humans). In some embodiments, a patient is a human. In some embodiments, a patient is suffering from or susceptible to one or more disorders or conditions. In some embodiments, a patient displays one or more symptoms of a disorder or condition. In some embodiments, a patient has been diagnosed with one or more disorders or conditions. In some embodiments, the disorder or condition is or includes cancer, or presence of one or more tumors. In some embodiments, the patient is receiving or has received certain therapy to diagnose and/or to treat a disease, disorder, or condition.

[0064] ***Peptide:*** The term "peptide" as used herein refers to a polypeptide that is typically relatively short, for example having a length of less than about 100 amino acids, less than about 50 amino acids, less than about 40 amino acids less than about 30 amino acids, less than about 25 amino acids, less than about 20 amino acids, less than about 15 amino acids, or less than 10 amino acids.

[0065] ***Pharmaceutical composition***: As used herein, the term "pharmaceutical composition" refers to a composition in which an active agent is formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, the active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments,a pharmaceutical composition may

be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces. In some embodiments, a pharmaceutical composition is intended and suitable for administration to a human subject. In some embodiments, a pharmaceutical composition is sterile and substantially pyrogen-free.

[0066] ***Pharmaceutically acceptable:*** As used herein, the term "pharmaceutically acceptable" applied to the carrier, diluent, or excipient used to formulate a composition as disclosed herein means that the carrier, diluent, or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

[0067] ***Pharmaceutically acceptable carrier:*** As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as

magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0068] ***Polypeptide:*** As used herein refers to any polymeric chain of amino acids. In some embodiments, a polypeptide has an amino acid sequence that occurs in nature. In some embodiments, a polypeptide has an amino acid sequence that does not occur in nature. In some embodiments, a polypeptide has an amino acid sequence that is engineered in that it is designed and/or produced through action of the hand of man. In some embodiments, a polypeptide may comprise or consist of natural amino acids, non-natural amino acids, or both. In some embodiments, a polypeptide may comprise or consist of only natural amino acids or only non-natural amino acids. In some embodiments, a polypeptide may comprise D-amino acids, L-amino acids, or both. In some embodiments, a polypeptide may comprise only D-amino acids. In some embodiments, a polypeptide may comprise only L-amino acids. In some embodiments, a polypeptide may include one or more pendant groups or other modifications, e.g., modifying or attached to one or more amino acid side chains, at the polypeptide's N-terminus, at the polypeptide's C-terminus, or any combination thereof. In some embodiments, such pendant groups or modifications may be selected from the group consisting of acetylation, amidation, lipidation, methylation, pegylation, etc., including combinations thereof. In some embodiments, a polypeptide may be cyclic, and/or may comprise a cyclic portion. In some embodiments, a polypeptide is not cyclic and/or does not comprise any cyclic portion. In some embodiments, a polypeptide is linear. In some embodiments, a polypeptide may be or comprise a stapled polypeptide. In some embodiments, the term "polypeptide" may be appended to a name of a reference polypeptide, activity, or structure; in such instances it is used herein to refer to polypeptides that share the relevant activity or structure and thus can be considered to be members of the same class or family of polypeptides. For each such class, the present specification provides and/or those skilled in the art will be aware of exemplary polypeptides within the class whose amino acid sequences and/or functions are known; in some embodiments, such exemplary polypeptides are reference polypeptides for the polypeptide class or family. In

some embodiments, a member of a polypeptide class or family shows significant sequence homology or identity with, shares a common sequence motif (e.g., a characteristic sequence element) with, and/or shares a common activity (in some embodiments at a comparable level or within a designated range) with a reference polypeptide of the class; in some embodiments with all polypeptides within the class). For example, in some embodiments, a member polypeptide shows an overall degree of sequence homology or identity with a reference polypeptide that is at least about 30-40%, and is often greater than about 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more and/or includes at least one region (e.g., a conserved region that may in some embodiments be or comprise a characteristic sequence element) that shows very high sequence identity, often greater than 90% or even 95%, 96%, 97%, 98%, or 99%. Such a conserved region usually encompasses at least 3-4 and often up to 20 or more amino acids; in some embodiments, a conserved region encompasses at least one stretch of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more contiguous amino acids. In some embodiments, a useful polypeptide may comprise or consist of a fragment of a parent polypeptide. In some embodiments, a useful polypeptide as may comprise or consist of a plurality of fragments, each of which is found in the same parent polypeptide in a different spatial arrangement relative to one another than is found in the polypeptide of interest (e.g., fragments that are directly linked in the parent may be spatially separated in the polypeptide of interest or vice versa, and/or fragments may be present in a different order in the polypeptide of interest than in the parent), so that the polypeptide of interest is a derivative of its parent polypeptide.

[0069] ***Prevent or Prevention***: The term "prevent" or "prevention", as used herein, refers to a delay of onset, and/or reduction in frequency and/or severity of one or more symptoms of a particular disease, disorder or condition. In some embodiments, prevention is assessed on a population basis such that an agent is considered to "prevent" a particular disease, disorder or condition if a statistically significant decrease in the development, frequency, and/or intensity of one or more symptoms of the disease, disorder or condition is observed in a population susceptible to the disease, disorder, or condition. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

[0070] ***Prognostic and predictive information:*** As used herein, the terms "prognostic information" and "predictive information" are used to refer to any information that may be used to indicate any aspect of the course of a disease or condition either in the absence or presence of treatment. Such information may include, but is not limited to, the average life expectancy of a patient, the likelihood that a patient will survive for a given amount of time (e.g., 6 months, 1 year, 5 years, etc.), the likelihood that a patient will be cured of a disease, the likelihood that a patient's disease will respond to a particular therapy (wherein response may be defined in any of a variety of ways). Prognostic and predictive information are included within the broad category of diagnostic information.

[0071] ***Protein:*** As used herein, the term "protein" refers to a polypeptide (*i.e.*, a string of at least two amino acids linked to one another by peptide bonds). Proteins may include moieties other than amino acids (*e.g.*, may be glycoproteins, proteoglycans, etc.) and/or may be otherwise processed or modified. Those of ordinary skill in the art will appreciate that a "protein" can be a complete polypeptide chain as produced by a cell (with or without a signal sequence), or can be a characteristic portion thereof. Those of ordinary skill will appreciate that a protein can sometimes include more than one polypeptide chain, for example linked by one or more disulfide bonds or associated by other means. Polypeptides may contain L-amino acids, D-amino acids, or both and may contain any of a variety of amino acid modifications or analogs known in the art. Useful modifications include, *e.g.*, terminal acetylation, amidation, methylation, etc. In some embodiments, proteins may comprise natural amino acids, non-natural amino acids, synthetic amino acids, and combinations thereof. The term "peptide" is generally used to refer to a polypeptide having a length of less than about 100 amino acids, less than about 50 amino acids, less than 20 amino acids, or less than 10 amino acids. In some embodiments, proteins are antibodies, antibody fragments, biologically active portions thereof, and/or characteristic portions thereof.

[0072] ***Reference***: As used herein, the term "reference" refers to a standard or control relative to which a comparison is performed. For example, in some embodiments, an agent, animal, individual, population, sample, sequence, or value of interest is compared to a reference or control agent, animal, individual, population, sample, sequence, or value. In some

embodiments, a reference or control is tested and/or determined substantially simultaneously with the testing or determination of interest. In some embodiments, a reference or control is a historical reference or control, optionally embodied in a tangible medium. Typically, as would be understood by those skilled in the art, a reference or control is determined or characterized under comparable conditions or circumstances to those under assessment. Those skilled in the art will appreciate when sufficient similarities are present to justify reliance on and/or comparison to a particular possible reference or control.

[0073] ***Response:*** As used herein, a response to treatment may refer to any beneficial alteration in a subject's condition that occurs as a result of or correlates with treatment. Such alteration may include stabilization of the condition (e.g., prevention of deterioration that would have taken place in the absence of the treatment), amelioration of symptoms of the condition, and/or improvement in the prospects for cure of the condition, etc. It may refer to a subject's response or to a tumor's response. Tumor or subject response may be measured according to a wide variety of criteria, including clinical criteria and objective criteria. Techniques for assessing response include, but are not limited to, clinical examination, positron emission tomatography, chest X-ray CT scan, MRI, ultrasound, endoscopy, laparoscopy, presence or level of tumor markers in a sample obtained from a subject, cytology, and/or histology. Many of these techniques attempt to determine the size of a tumor or otherwise determine the total tumor burden. Methods and guidelines for assessing response to treatment are discussed in Therasse et. al., "New guidelines to evaluate the response to treatment in solid tumors", European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada, *J. Natl. Cancer Inst.*, 2000, 92(3):205-216. The exact response criteria can be selected in any appropriate manner, provided that when comparing groups of tumors and/or patients, the groups to be compared are assessed based on the same or comparable criteria for determining response rate. One of ordinary skill in the art will be able to select appropriate criteria.

[0074] ***Sample:*** As used herein, the term "sample" refers to a biological sample obtained or derived from a source of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as a microbe, a plant, an animal or a human. In some

embodiments, a biological sample comprises biological tissue or fluid. In some embodiments, a biological sample may comprise bone marrow; blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid, peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or broncheoalveolar lavages; aspirates; scrapings; bone marrow specimens; tissue biopsy specimens; surgical specimens; other body fluids, secretions, and/or excretions; and/or cells therefrom. In some embodiments, a biological sample comprises cells obtained from an individual, *e.g.*, from a human or animal subject. In some embodiments, obtained cells are or include cells from an individual from whom the sample is obtained. In some embodiments, a sample is a "primary sample" obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group consisting of biopsy (*e.g.*, fine needle aspiration or tissue biopsy), surgery, collection of body fluid (*e.g.*, blood, lymph, feces). In some embodiments, as will be clear from context, the term "sample" refers to a preparation that is obtained by processing (*e.g.*, by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a "processed sample" may comprise, for example nucleic acids or polypeptides extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components.

[0075] ***Subject:*** As used herein, the term "subject" refers to an organism, for example, a mammal (*e.g.*, a human, a non-human mammal, a non-human primate, a primate, a laboratory animal, a mouse, a rat, a hamster, a gerbil, a cat, a dog). In some embodiments a human subject is an adult, adolescent, or pediatric subject. In some embodiments, a subject is suffering from a disease, disorder or condition, *e.g.*, a disease, disorder or condition that can be treated as provided herein, *e.g.*, a cancer or a tumor listed herein. In some embodiments, a subject is susceptible to a disease, disorder, or condition; in some embodiments, a susceptible subject is predisposed to and/or shows an increased risk (as compared to the average risk observed in a reference subject or population) of developing the disease, disorder or condition. In some

embodiments, a subject displays one or more symptoms of a disease, disorder or condition. In some embodiments, a subject does not display a particular symptom (*e.g,*. clinical manifestation of disease) or characteristic of a disease, disorder, or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

[0076] ***Substantially:*** As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0077] ***Susceptible to***: An individual who is "susceptible to" a disease, disorder, or condition (*e.g.*, influenza) is at risk for developing the disease, disorder, or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition does not display any symptoms of the disease, disorder, or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition has not been diagnosed with the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition is an individual who has been exposed to conditions associated with development of the disease, disorder, or condition. In some embodiments, a risk of developing a disease, disorder, and/or condition is a population-based risk (e.g., family members of individuals suffering from the disease, disorder, or condition).

[0078] ***Symptoms are reduced:*** According to the present invention, "symptoms are reduced" when one or more symptoms of a particular disease, disorder or condition is reduced in magnitude (*e.g.*, intensity, severity, *etc.*) and/or frequency. For purposes of clarity, a delay in the onset of a particular symptom is considered one form of reducing the frequency of that symptom.

[0079] ***Therapeutic regimen***: A "therapeutic regimen", as that term is used herein, refers to a dosing regimen whose administration across a relevant population may be correlated with a desired or beneficial therapeutic outcome.

[0080] ***Therapeutic agent***: As used herein, the term "therapeutic agent" in general refers to any agent that elicits a desired effect (*e.g.,* a desired biological, clinical, or pharmacological effect) when administered to a subject. In some embodiments, an agent is considered to be a therapeutic agent if it demonstrates a statistically significant effect across an appropriate population. In some embodiments, an appropriate population is a population of subjects suffering from and/or susceptible to a disease, disorder or condition. In some embodiments, an appropriate population is a population of model organisms. In some embodiments, an appropriate population may be defined by one or more criterion such as age group, gender, genetic background, preexisting clinical conditions, prior exposure to therapy. In some embodiments, a therapeutic agent is a substance that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms or features of a disease, disorder, and/or condition in a subject when administered to the subject in an effective amount. In some embodiments, a "therapeutic agent" is an agent that has been or is required to be approved by a government agency before it can be marketed for administration to humans. In some embodiments, a "therapeutic agent" is an agent for which a medical prescription is required for administration to humans.

[0081] ***Therapeutically effective amount:*** As used herein, is meant an amount that produces the desired effect for which it is administered. In some embodiments, the term refers to an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, and/or condition in accordance with a therapeutic dosing regimen, to treat the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence and/or severity of, and/or delays onset of, one or more symptoms of the disease, disorder, and/or condition. Those of ordinary skill in the art will appreciate that the term "*therapeutically effective amount*" does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of

subjects when administered to patients in need of such treatment. In some embodiments, reference to a therapeutically effective amount may be a reference to an amount as measured in one or more specific tissues (e.g., a tissue affected by the disease, disorder or condition) or fluids (e.g., blood, saliva, serum, sweat, tears, urine, etc.). Those of ordinary skill in the art will appreciate that, in some embodiments, a therapeutically effective amount of a particular agent or therapy may be formulated and/or administered in a single dose. In some embodiments, a therapeutically effective agent may be formulated and/or administered in a plurality of doses, for example, as part of a dosing regimen.

[0082] ***Treatment***: As used herein, the term "treatment" (also "treat" or "treating") refers to any administration of a therapy that partially or completely alleviates, ameliorates, relives, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition. In some embodiments, such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, and/or condition.

[0083] ***Unit dose***: The expression "unit dose" as used herein refers to an amount administered as a single dose and/or in a physically discrete unit of a pharmaceutical composition. In many embodiments, a unit dose contains a predetermined quantity of an active agent. In some embodiments, a unit dose contains an entire single dose of the agent. In some embodiments, more than one unit dose is administered to achieve a total single dose. In some embodiments, administration of multiple unit doses is required, or expected to be required, in order to achieve an intended effect. A unit dose may be, for example, a volume of liquid (e.g., an acceptable carrier) containing a predetermined quantity of one or more therapeutic agents, a predetermined amount of one or more therapeutic agents in solid form, a sustained release

formulation or drug delivery device containing a predetermined amount of one or more therapeutic agents, etc. It will be appreciated that a unit dose may be present in a formulation that includes any of a variety of components in addition to the therapeutic agent(s). For example, acceptable carriers (e.g., pharmaceutically acceptable carriers), diluents, stabilizers, buffers, preservatives, etc., may be included as described infra. It will be appreciated by those skilled in the art, in many embodiments, a total appropriate daily dosage of a particular therapeutic agent may comprise a portion, or a plurality, of unit doses, and may be decided, for example, by the attending physician within the scope of sound medical judgment. In some embodiments, the specific effective dose level for any particular subject or organism may depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of specific active compound employed; specific composition employed; age, body weight, general health, sex and diet of the subject; time of administration, and rate of excretion of the specific active compound employed; duration of the treatment; drugs and/or additional therapies used in combination or coincidental with specific compound(s) employed, and like factors well known in the medical arts.

[0084] ***Vaccination***: As used herein, the term "vaccination" refers to the administration of a composition intended to generate an immune response, for example to a disease-causing agent. For the purposes of the present invention, vaccination can be administered before, during, and/or after exposure to a disease-causing agent, and in certain embodiments, before, during, and/or shortly after exposure to the agent. In some embodiments, vaccination includes multiple administrations, appropriately spaced in time, of a vaccinating composition.

DETAILED DESCRIPTION OF THE INVENTION

[0085] This application describes a combination therapy comprising an immunogenic composition against HSV-2 and an antiviral therapy. HSV-2 is a common cause of genital herpes and one of the most common sexually transmitted diseases with nearly 500 million people affected worldwide. Evidence of infection, by serologic studies, is present in 1 out of every 6 people aged 14 to 49 in the United States. Women are more commonly infected than men, with

1 out of every 5 women in the US having evidence of infection. Certain groups, such as people with human immunodeficiency virus (HIV) and commercial sex workers, have high rates of infection ranging from 60% to 95%, (Kimberlin & Rouse, New Engl J Med. (2004) 350:1970–7; Gupta et al., Lancet. (2007) 370:2127–37)

[0086] HSV-2 infection is associated with a 3-fold increase in risk of acquiring HIV infection, due in part to the presence of herpetic lesions (which may result in breach of the genital epithelium) and is considered to be a substantial contributor to the worldwide AIDS epidemic (Corey, J Infect Dis. (2007) 195:1242–4; Freeman et al., AIDS (2006) 20:73-83). Most HSV-2 seropositive people are unaware of their infection status, probably because of mild and atypical symptoms and signs, and this lack of awareness contributes to the continued spread of HSV-2 infection among susceptible populations.

[0087] In people with recognized genital herpes, the disease is characterized by the development of vesicles at the site of infection, usually the anogenital region (defined as the area covered by boxer shorts). Vesicles persist for days and evolve to ulcers that eventually crust and heal. The initial clinical manifestations occur approximately 4 days after acquisition of infection and are referred to as the primary outbreak or infection (or nonprimary initial, for the first episode of HSV-2 in a patient who is herpes simplex type 1 [HSV-1] seropositive). In the absence of antiviral therapy, lesions resolve over the course of 1 to 3 weeks. The virus migrates in a retrograde process to become latent in the sensory nerve ganglia. At varying intervals, recurrences (secondary outbreaks or infections) develop when the virus travels anterograde to the skin or mucosal surfaces. During the first year after primary infection, the median recurrence rate in the absence of therapy is 4 per year, and 20% of patients experience more than 10 recurrences (Benedetti et al., Ann Intern Med (1994) 121:847–54).

[0088] HSV-2 infection is transmitted by contact with the mucosal membranes of an infected person who is shedding the virus. During clinically active recurrences (presence of genital ulcers) HSV-2 can frequently be detected in ulcers and the surrounding skin and mucosa. However, during asymptomatic periods, shedding of HSV-2 from the anogenital regions of an infected person can be detected on approximately 10% to 13% of days (subclinical shedding) by polymerase chain reaction (PCR) (Fife et al., Mayo Clin Proc. (2006) 81:1321–7; Martens et al.,

Infect Dis Obstet Gynecol (2009) 105376). Most transmission occurs during such periods of subclinical shedding. Transmission may also occur from pregnant mother to infant at birth, resulting in a severe form of disseminated infection leading to permanent neurologic damage or death of the infant (Whitley, Curr Opin Infect Dis. (2004) 17:243–6).

[0089] For these indications, acyclovir, valacyclovir, or famciclovir can be effective. Both clinical and subclinical shedding of HSV-2 are reduced, but not eliminated, during periods of therapy (Wald et al., Ann Intern Med. (1996) 124:8–15; Gupta et al., J Infect Dis. (2004) 190:1374–81; Fife et al., Mayo Clin Proc. (2006) 81:1321–7; Martens et al., Infect Dis Obstet Gynecol (2009) 105376; Johnston et al., Lancet. (2012) 379:641–7). However, in a clinical trial valacyclovir reduced transmission of HSV-2 from infected persons to uninfected partners by only 48% (Corey et al., J Infect Dis. (2007) 195:1242–4). The limitations of antiviral therapy include the requirement for daily treatment, potentially incomplete compliance leading to breakthrough of viral shedding or clinical disease, inability to completely suppress clinical recurrences, and limited prevention of transmission of infection. Consequently, there have been a number of attempts to develop effective vaccines either for prevention or treatment of infection with HSV-2 (Stanberry et al., N Engl J Med. (2002) 347:1652–61; de Bruyn et al., Vaccine. (2006) 24:914–20), but none is currently available. Thus, new and improved methodologies for herpesvirus vaccine discovery are needed to protect against herpes diseases.

Immunogenic Compositions

[0090] Immunogenic compositions for use in combination with antiviral therapy 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 an immunogenic composition comprise the entire sequence of at least one of SEQ ID NOS: 1-26, 135, 136, 138 and 139, or consist of the entire sequence of any one of SEQ ID NOS: 1-26, 135, 136, 138 and 139. Immunogenic compositions may include a polypeptide comprising a sequence from Table 1 or Table 2 or an immunogenic fragment thereof or a combination of at least two polypeptides comprising sequences from Table 1 or Table 2, or immunogenic fragments thereof. In certain embodiments, the polypeptide(s) of the immunogenic compositions comprise the entire sequence

of any one of SEQ ID NOS: 1-38, 135, 136, 138 and 139 or consist of the entire sequence of any one of SEQ ID NO: 1-38, 135, 136, 138 and 139. The polypeptides in Tables 1 or 2 may be encoded by SEQ ID NOS: 39-46 and 117-134, 137, 140 and 141 as indicated and/or by cDNA sequences publically available on www.ncbi.nlm.nih.gov/sites/entrez. cDNA and protein sequences may also be obtained from any known strains of HSV-2, including HG52, 333, and Strain G. Accordingly, cDNA sequences may be accessed by gene or protein name from genomic sequence at NC_001798.1, and may be approximately 97% conserved with sequences disclosed at NC_001798.1. As described herein, the polypeptides may be referred to by protein name, by SEQ ID NO, and/or by the name of the gene encoding the protein.

[0091] The polypeptides can be prepared in a variety of expression systems. Suitable expression systems include *E. coli* and Baculovirus-based expression systems (*e.g.*, in insect cells). Polypeptides prepared using *E. coli* are typically full-length and unglycosylated, although truncated variants can be prepared. In certain embodiments, these truncated variants retain all or part of the signal domain. Polypeptides prepared using a Baculovirus system typically lack the N-terminal signal sequence, but are fully or partially glycosylated.

[0092] In some embodiments, the polypeptides are prepared in non-mammalian cell systems. When an exogenous signal sequence is used, polypeptides may contain one or more amino acids at the N-terminal end which correspond to the exogenous signal sequence. An exogenous signal sequence commonly used in insect expression systems is the honey bee mellitin signal sequence. In other embodiments, the polypeptides may contain one or more amino acids corresponding to a signal sequence that has been cleaved. Exemplary polypeptides may contain one or more amino acids from a mammalian signal sequence that has been left intact or cleaved off, depending on the system used to prepare the polypeptides.

Table 1. HSV-2 antigens for immunogenic compositions

Protein SEQ ID No.	DNA SEQ ID No.	Gene or Construct Name *Protein Name*	GeneID No.	GenBank Accession Nos.
1	39	RS1 *ICP4*	1487291 (duplicated in HSV-2 genome: also 1487290)	NP_044530.1 (duplicated in HSV-2 genome: also NP_044544.1)
2	117	RS1.2 *ICP4 internal fragment (ICP4.2)*	1487291	NP_044530.1 RS1.2 corresponds to an amino acid sequence of an internal fragment of an RS1 sequence
3	118	UL1 *gL2 cytoplasmic*	1487292	NP_044470.1
4	40	US6ΔTMR *gD2 internal deletion (gD2ΔTMR)*	1487358	NP_044536.1 US6ΔTMR corresponds to gD2 with a deletion of amino acids 340-363
5		US6 *gD2*	1487358	NP_044536.1
6	41	RL1 *ICP34.5*	1487287	NP_044529.1
7	42	RL2 *ICP0*	1487289	NP_044528.2
8	121	RS1.1 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.1 corresponds to residues 1-400 of RS1
9	122	RS1.3.1 *ICP4 internal*	1487291	NP_044530.1 RS1.3.1 corresponds to residues 750-1024 of RS1

Protein SEQ ID No.	DNA SEQ ID No.	Gene or Construct Name *Protein Name*	GeneID No.	GenBank Accession Nos.
		fragment		
10	123	RS1.3.2 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.3.2 corresponds to residues 1008-1319 of RS1
11	124	RS1.3 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.3 corresponds to residues 750-1319_of RS1
12	125	RS1.4 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.4 corresponds to residues 340-883 of RS1
13	126	RS1.5 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.5 corresponds to residues 775-1318 of RS1
14	127	RS1.6 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.6 corresponds to residues 210-1318 of RS1
15	128	RS1.7 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.7 has a deletion of residues 391-544 of RS1
16	129	RS1.8 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.8 has a deletion of residues 786-868 of RS1
17		UL2 v.1 *uracil DNA*	1487303	NP_044471.2

Protein SEQ ID No.	DNA SEQ ID No.	Gene or Construct Name *Protein Name*	GeneID No.	GenBank Accession Nos.
		glycosylase		
135		UL2 v.2 *uracil DNA glycosylase*	1487303	NP_044471.2
18		UL11 *myristylated tegument protein*	1487294	NP_044480.1
19	119	UL1s v.1 *gL2 secreted*	1487292	NP_044470.1
136	137	UL1s v.2 *gL2 secreted*	1487292	NP_044470.1
20		UL19a *VP5*	1487302	NP_044488.1
21	120	UL19ΔTEV *VP5*	1487302	NP_044488.1
22		UL36 *ICP1/2*	1487322	NP_044506.1
23	43	UL36.3.4.1 *ICP1/2 internal fragment*	1487322	NP_044506.1 UL 36.3.4.1 corresponds to residues 1318-2280 of UL36
24	44	UL36.4.2.5 *ICP1/2 internal*	1487322	NP_044506.1 UL 36.4.2.5 corresponds to residues 2253-3122 of UL36

Protein SEQ ID No.	DNA SEQ ID No.	Gene or Construct Name *Protein Name*	GeneID No.	GenBank Accession Nos.
		fragment		
25		UL40 *ribonucleoside reductase*	1487327	NP_044510.1
26	45	US12 *ICP47*	1487353	NP_044543.1
138	140	RS1.9 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.9 has a deletion of residues 391-544 and 786-821 of RS1
139	141	RS1.10 *ICP4 internal fragment*	1487291	NP_044530.1 RS1.10 has a deletion of residues 391-508 and 786-821 of RS1

Table 2. Additional HSV-2 antigens for immunogenic compositions

Protein SEQ ID No.	DNA SEQ ID No.	Gene or Construct Name *Protein Name*	GeneID No.	GenBank Accession Nos.
27	134	UL10 *gM2*	1487293	NP_044479.1
28		UL15 *DNA cleavage/packaging protein*	1487298	NP_044484.1

Protein SEQ ID No.	DNA SEQ ID No.	Gene or Construct Name *Protein Name*	GeneID No.	GenBank Accession Nos.
29		UL26.5 *ICP35*	1487311	NP_044496.1
30		UL30 *DNA-directed polymerase*	1487316	NP_044500.1
31		UL5 *DNA helicase/primase complex*	1487338	NP_044474.1
32		UL8 *DNA helicase/primase complex*	1487348	NP_044477.1
33		UL15.5 *unknown*	1487298	NP_044484.1 UL15.5 is an alternate translation of UL15
34		UL32 *cleavage/packaging protein*	1487318	NP_044502.1

Protein SEQ ID No.	DNA SEQ ID No.	Gene or Construct Name *Protein Name*	GeneID No.	GenBank Accession Nos.
35		UL36.4.2 *ICP1/2 fragment*	1487322	NP_044506.1
36		UL54 *ICP27*	1487343	NP_044525.1
37	133	UL49.5 *membrane-associated virion protein*	1487337	NP_044520.1
38	46	US4 *gG2*	1487356	NP_044534.1

Immunogenic HSV-2 polypeptides

[0093] Immunogenic polypeptides or polynucleotides as indicated in Table 1 and/or Table 2 may be used in immunogenic compositions, e.g., pharmaceutical compositions. The disclosure provides immunogenic compositions containing immunogenic polypeptides or polynucleotides encoding these immunogenic polypeptides, e.g., together with a pharmaceutical carrier. Antigens from HSV-2 may be identified by screening immune cells from patients exposed to or infected with HSV-2. Briefly, a library of HSV-2 antigens was expressed by bacteria and mixed with APCs. The APCs, in turn, processed and presented HSV-2-derived peptides to lymphocytes that had been isolated from human patients exposed to or infected with HSV-2. The patients belonged to several populations: (1) exposed to HSV-2 but seronegative for infection, (2) infected with HSV-2 but asymptomatic, (3) infected with HSV-2 and experiencing infrequent outbreaks, (4) infected with HSV-2 and experiencing frequent outbreaks, (5) naïve

and (6) seronegative for HSV-2 (HSV-2$^-$) but seropositive for HSV-1 (HSV-1$^+$). Lymphocyte responses from each population were compared for reactivity to HSV-2-derived polypeptides, and the screen detected antigens that induced reactive lymphocytes with greater frequency in one patient population as compared to the others. Infected but asymptomatic, and exposed but seronegative patients may activate protective immune responses that patients who experience frequent outbreaks do not; in particular, exposed but seronegative patients are presumed to have mounted sterilizing immunity to HSV-2 infection. It is believed that a unique set of polypeptides will activate lymphocytes from these patient populations. Thus, the present invention contemplates compositions of the specific HSV-2 polypeptides that activate the lymphocytes of infected but asymptomatic, or exposed but seronegative patients or a combination of these polypeptides for inhibiting or counteracting infection by HSV-2.

[0094] Antigens identified on the basis of their immunogenicity in infected but asymptomatic, or exposed but seronegative patients, are similarly expected to be immunogenic in any subject.

[0095] In some embodiments, a polypeptide may induce an innate immune response, a humoral immune response, or a cell-mediated immune response. The cell-mediated immune response may involve CD4+ and/or CD8+ T cells, and in certain embodiments, the immune response involving CD4+ T cells is an immune response in which TH1 cells are activated. In some embodiments, an immunogenic polypeptide avoids induction of TH2 cytokines. In some embodiments, the immune response involving CD4+ T cells is an immune response in which TH17 cells are activated.

[0096] Polypeptides (or immunogenic fragments thereof) in immunogenic compositions of the disclosure may induce T cell responses in multiple individuals, regardless of the HLA haplotype of the individuals. Specifically, epitopes in the polypeptides may induce T cell responses in individuals with one or more of the following HLA supertypes: HLA-A2, -A3, -A24, -A1, -B7, -B8, -B27, -B44, -B58, and B62, and HLA-DQB01, -DQB02, -DQB03, -DQB-04, and -DQB05.

[0097] In some embodiments, one or more, *e.g.* two, three, four, or more polypeptides from Table 1 and/or Table 2 (or immunogenic fragments thereof) are provided in an immunogenic composition. In some embodiments, two polypeptides from Table 1 and/or Table 2 are provided in an immunogenic composition. In other embodiments, three polypeptides from Table 1 and/or Table 2 are provided in an immunogenic composition. In other embodiments, four polypeptides from Table 1 and/or Table 2 are provided in an immunogenic composition.

[0098] In some embodiments, two, three, four, or more polypeptides from Table 1 and/or Table 2 (or immunogenic fragments thereof) are provided together as a conjugate. In some embodiments, two polypeptides from Table 1 and/or Table 2, or three polypeptides from Table 1 and/or Table 2, or four polypeptides from Table 1 and/or Table 2, are provided as a conjugate. In some embodiments, two, three, four, or more polypeptides from Table 1 and/or Table 2 are covalently bound to each other, e.g., as a fusion protein. In some embodiments, two polypeptides from Table 1 and/or Table 2, or three polypeptides from Table 1 and/or Table 2, or four polypeptides from Table 1 and/or Table 2, are covalently bound to each other, e.g. as a fusion protein.

[0099] In some embodiments, an immunogenic composition comprises two, three, four, or more polypeptides selected from the group consisting of SEQ ID NOS: 1-38, 135, 136, 138 and 139, and may contain or may not contain any other HSV-2 polypeptides.

[0100] In certain embodiments, an immunogenic composition comprises one or more polypeptides that are at least 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a polypeptide encoded by a gene in Table 1 and/or Table 2, or a portion of said polypeptide. In certain embodiments, the homologous polypeptide is at least 8, 10, 15, 20, 30, 40, 50, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, such as those described immediately above, the polypeptide is no more than 300, 350, 400, 450, or 500 amino acids in length.

[0101] An immunogenic composition may also comprise portions of said polypeptides and genes, for example deletion mutants, truncation mutants, oligonucleotides, and peptide fragments. In some embodiments, the portions of said proteins are immunogenic.

[0102] The immunogenicity of a portion of a protein or a homolog thereof can be readily determined using the same assays that are used to determine the immunogenicity of the full-length protein. In some embodiments, the portion of the protein has substantially the same immunogenicity as the full-length proteins. In some embodiments, the immunogenicity is no more than 10%, 20%, 30%, 40%, or 50% less than that of the full-length protein. The protein fragments may be, for example, linear, circular, or branched. In some embodiments, a protein or protein fragment comprises one or more non-natural amino acids (*e.g.* an amino acid other than the 20 typically found in natural proteins). A non-natural amino acid may have an atypical side chain. In addition, peptidomimetics may be used; these may incorporate alterations to the peptide backbone.

[0103] In some embodiments, an immunogenic composition described herein includes an immunogenic polypeptide that contains a membrane translocating sequence (MTS), to facilitate introduction of the polypeptide into the mammalian cell and subsequent stimulation of the cell-mediated immune response. Exemplary membrane translocating sequences include hydrophobic region in the signal sequence of Kaposi fibroblast growth factor, the MTS of α-synuclein, β-synuclein, or γ-synuclein, the third helix of the Antennapedia homeodomain, SN50, integrin β3 h-region, HIV Tat, pAntp, PR-39, abaecin, apidaecin, Bac5, Bac7, *P. berghei* CS protein, and those MTSs described in US Patents 6,248,558, 6,432,680 and 6,248,558.

[0104] In certain embodiments, an immunogenic polypeptide is conjugated (e.g., covalently bound) to another molecule. This may, for example, increase the half-life, solubility, bioavailability, or immunogenicity of the antigen. Molecules that may be conjugated to an immunogenic polypeptide include a carbohydrate, biotin, poly(ethylene glycol) (PEG), polysialic acid, N-propionylated polysialic acid, nucleic acids, polysaccharides, and PLGA. There are many different types of PEG, ranging from molecular weights of below 300 g/mol to over 10,000,000 g/mol. PEG chains can be linear, branched, or with comb or star geometries.

Immunogenic HSV-2 polypeptides and nucleic acids for use in immunogenic compositions

[0105] In certain embodiments, one or more, *e.g.* two, three, four, or more immunogenic fragments or variants thereof are provided in a mixture. For example, an immunogenic composition may comprise any one or more of SEQ ID NOS: 1-26, 136, 138 or 139.

[0106] In certain embodiments, an immunogenic composition may comprise any one, two, three, or four of ICP4, ICP4.2, ICP4.5, ICP4.9, ICP4.10, gL2, gL2s v.2, gD2ΔTMR and gD2 (SEQ ID NOS: 1-5, 13, 136, 138 and 139), or immunogenic fragment(s) thereof. In certain embodiments, combinations contain polypeptides or immunogenic fragments from only one of ICP4 (SEQ ID NO: 1), ICP4.2 (SEQ ID NO: 2), ICP4.5 (SEQ ID NO: 13), ICP4.9 (SEQ ID NO: 138) and ICP4.10 (SEQ ID NO: 139). In other embodiments, combinations contain polypeptides or immunogenic fragments from only one of gD2ΔTMR (SEQ ID NO: 4) and gD2 (SEQ ID NO: 5). In yet other embodiments, combinations contain polypeptides or immunogenic fragments from only one of gL2 (SEQ ID NO: 3) and gL2s v.2s (SEQ ID NO: 136). In some embodiments, combinations contain polypeptides or immunogenic fragments from any two of ICP4.2 (SEQ ID NO: 2), ICP4.5 (SEQ ID NO: 13), ICP4.9 (SEQ ID NO: 138) and ICP4.10 (SEQ ID NO: 139).

[0107] In some embodiments, an immunogenic composition may comprise at least one polypeptide fragment of SEQ ID NO: 1, such as the polypeptides of SEQ ID NOS: 2, 8-16, 138 and 139. In some embodiments, an immunogenic composition may comprise at least two polypeptide fragments of SEQ ID NO: 1, such as the polypeptides of SEQ ID NOS: 2, 8-16, 138 and 139. One or more polypeptide fragments of SEQ ID NO: 1 may replace SEQ ID NO: 1 in any of the immunogenic compositions as described herein.

[0108] Exemplary combinations of ICP4, ICP4.2, ICP4.5, ICP4.9, ICP4.10, gL2, gL2s v.2, gD2ΔTMR and gD2 include:

Two antigen combinations	
ICP4 SEQ ID NO: 1	gL2 or gL2s v.2 SEQ ID NO: 3 or SEQ ID NO: 136
ICP4 SEQ ID NO: 1	gD2ΔTMR SEQ ID NO: 4

ICP4 SEQ ID NO: 1	gD2 SEQ ID NO: 5
ICP4.2 SEQ ID NO: 2	gL2 or gL2s v.2 SEQ ID NO: 3 or SEQ ID NO: 136
ICP4.2 SEQ ID NO: 2	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	gD2 SEQ ID NO: 5
gL2 or gL2s v.2 SEQ ID NO: 3 or SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
gL2 or gL2s v.2 SEQ ID NO: 3 or SEQ ID NO: 136	gD2 SEQ ID NO: 5
ICP4.5 SEQ ID NO: 13	gL2 or gL2s v.2 SEQ ID NO: 3 or SEQ ID NO: 136
ICP4.5 SEQ ID NO: 13	gD2ΔTMR SEQ ID NO: 4
ICP4.5 SEQ ID NO: 13	gD2 SEQ ID NO: 5
ICP4.9 SEQ ID NO: 138	gL2 or gL2s v.2 SEQ ID NO: 3 or SEQ ID NO: 136
ICP4.9 SEQ ID NO: 138	gD2ΔTMR SEQ ID NO: 4
ICP4.9	gD2

SEQ ID NO: 138	SEQ ID NO: 5
ICP4.10 SEQ ID NO: 139	gL2 or gL2s v.2 SEQ ID NO: 3 or SEQ ID NO: 136
ICP4.10 SEQ ID NO: 139	gD2ΔTMR SEQ ID NO: 4
ICP4.10 SEQ ID NO: 139	gD2 SEQ ID NO: 5

Three antigen combinations		
ICP4 SEQ ID NO: 1	gL2 SEQ ID NO: 3	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	gL2 SEQ ID NO: 3	gD2ΔTMR SEQ ID NO: 4
ICP4.5 SEQ ID NO: 13	gL2 SEQ ID NO: 3	gD2ΔTMR SEQ ID NO: 4
ICP4.9 SEQ ID NO: 138	gL2 SEQ ID NO: 3	gD2ΔTMR SEQ ID NO: 4
ICP4.10 SEQ ID NO: 139	gL2 SEQ ID NO: 3	gD2ΔTMR SEQ ID NO: 4
ICP4	gL2	gD2

SEQ ID NO: 1	SEQ ID NO: 3	SEQ ID NO: 5
ICP4.2 SEQ ID NO: 2	gL2 SEQ ID NO: 3	gD2 SEQ ID NO: 5
ICP4.5 SEQ ID NO: 13	gL2 SEQ ID NO: 3	gD2 SEQ ID NO: 5
ICP4.9 SEQ ID NO: 138	gL2 SEQ ID NO: 3	gD2 SEQ ID NO: 5
ICP4.10 SEQ ID NO: 139	gL2 SEQ ID NO: 3	gD2 SEQ ID NO: 5
ICP4 SEQ ID NO: 1	gL2s v.2 SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	gL2s v.2 SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
ICP4.5 SEQ ID NO: 13	gL2s v.2 SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
ICP4.9 SEQ ID NO: 138	gL2s v.2 SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
ICP4.10 SEQ ID NO: 139	gL2s v.2 SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
ICP4 SEQ ID NO: 1	gL2s v.2 SEQ ID NO: 136	gD2 SEQ ID NO: 5

ICP4.2 SEQ ID NO: 2	gL2s v.2 SEQ ID NO: 136	gD2 SEQ ID NO: 5
ICP4.5 SEQ ID NO: 13	gL2s v.2 SEQ ID NO: 136	gD2 SEQ ID NO: 5
ICP4.9 SEQ ID NO: 138	gL2s v.2 SEQ ID NO: 136	gD2 SEQ ID NO: 5
ICP4.10 SEQ ID NO: 139	gL2s v.2 SEQ ID NO: 136	gD2 SEQ ID NO: 5

Four antigen combinations			
ICP4.2 SEQ ID NO: 2	ICP4.5 SEQ ID NO: 13	gL2 SEQ ID NO: 3	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	ICP4.9 SEQ ID NO: 138	gL2 SEQ ID NO: 3	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	ICP4.10 SEQ ID NO: 139	gL2 SEQ ID NO: 3	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	ICP4.5 SEQ ID NO: 13	gL2 SEQ ID NO: 3	gD2 SEQ ID NO: 5
ICP4.2	ICP4.9 SEQ ID NO:	gL2	gD2

SEQ ID NO: 2	138	SEQ ID NO: 3	SEQ ID NO: 5
ICP4.2 SEQ ID NO: 2	ICP4.10 SEQ ID NO: 139	gL2 SEQ ID NO: 3	gD2 SEQ ID NO: 5
ICP4.2 SEQ ID NO: 2	ICP4.5 SEQ ID NO: 13	gL2s v.2 SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	ICP4.9 SEQ ID NO: 138	gL2s v.2 SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	ICP4.10 SEQ ID NO: 139	gL2s v.2 SEQ ID NO: 136	gD2ΔTMR SEQ ID NO: 4
ICP4.2 SEQ ID NO: 2	ICP4.5 SEQ ID NO: 13	gL2s v.2 SEQ ID NO: 136	gD2 SEQ ID NO: 5
ICP4.2 SEQ ID NO: 2	ICP4.9 SEQ ID NO: 138	gL2s v.2 SEQ ID NO: 136	gD2 SEQ ID NO: 5
ICP4.2 SEQ ID NO: 2	ICP4.10 SEQ ID NO: 139	gL2s v.2 SEQ ID NO: 136	gD2 SEQ ID NO: 5

[0109] The individual antigens and combinations described above can also include additional peptides from or derived from HSV-2, such as polypeptides comprising sequences

selected from SEQ ID NOS: 6-12, 14-26, and SEQ ID NO: 135, or immunogenic fragments thereof.

[0110] In some embodiments, the individual antigens and combinations described above are provided as isolated nucleic acids. In certain aspects, the nucleic acids have the nucleotide sequence of at least one of SEQ ID NOS: 39-45, 117-129, 137, 140, 141, or an immunogenic fragment thereof. Nucleic acids can be present in compositions of the invention singly or in combinations. Exemplary combinations include nucleic acids encoding for two or more of ICP4 (SEQ ID NO: 1), ICP4.9 (SEQ ID NO: 138), gL2 (SEQ ID NO: 3), gG2 (SEQ ID NO: 38) and gD2 (SEQ ID NO: 5).

ICP4 (SEQ ID NO: 1) encoded by RS1

[0111] RS1 encodes ICP4, a transcriptional transactivator that may interact with and recruit specific components of the general transcription machinery to viral promoters and stabilize their formation for transcription initiation. ICP4 contains distinct domains for transactivation/phosphorylation (approximately spanning amino acid residues 150-200 of SEQ ID NO: 1), DNA binding (approximately spanning residues 380-540 of SEQ ID NO: 1), nuclear localization (approximately spanning residues 630-730 of SEQ ID NO: 1), and late regulatory transactivation (approximately spanning residues 1220-1319 of SEQ ID NO: 1). The DNA and protein sequence of RS1 may be found by searching for RS1 in the publicly available database, Entrez Gene (on the NCBI NIH web site on the World Wide Web, at www.ncbi.nlm.nih.gov/sites/entrez?db=gene), in the Human herpesvirus 2 complete genome.

[0112] In some embodiments, an immunogenic composition described herein includes a polypeptide containing at least 20 consecutive amino acid residues selected from residues 383-766 of ICP4 (SEQ ID NO: 1), but no more than 1000 amino acids of ICP4 (SEQ ID NO: 1). The polypeptide may also be a variant of the at least 20 residue fragment.

[0113] In certain embodiments, the polypeptide includes no more than 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450 or even 400 consecutive amino acids from ICP4. Exemplary polypeptides correspond approximately to amino acids residues of full-length ICP4

as follows: 383-766; 1-400 (RS1.1); 750-1024 (RS1.3.1); 1008-1319 (RS1.3.2); 750-1319 (RS1.3); 280-785 (RS1.4 comprising the full DNA binding region); 680-1319 (RS1.5 comprising the glycosylase/C-terminal region); 208-1319 (RS1.6 which may also comprise a Met residue at the N-term end); 1-380 plus 545-1319 (RS1.7, in which a region spanning approximately residues 381-544 is deleted, removing the DNA binding regions); 1-785 plus 870-1319 (RS1.8, in which a region spanning approximately residues 786-869 is deleted, removing the nuclear localization domain), or 1-766, 383-1318, 100-750, 400-1300, 250-766, 383-900 of ICP4 (SEQ ID NO: 1) and the like.

ICP4 internal fragment ICP4.2 (SEQ ID NO: 2) encoded by RS1.2

[0114] RS1.2 encodes a 391 amino acid fragment denoted ICP4.2.

[0115] In specific embodiments, an immunogenic composition described herein includes a polypeptide containing from 50 to all 391 amino acids residues of ICP4.2 (SEQ ID NO: 2), such as from 100 to 391, 200 to 391 or 250 to 350 residues. In particular embodiments, the polypeptide includes all of ICP4.2 (SEQ ID NO: 2) or is ICP4.2 (SEQ ID NO: 2) itself. These polypeptides may, for example, include the full length or fragments of ICP4.2 (SEQ ID NO: 2) described herein with amino acid residues 1-382 or 767-1318 of ICP4 (SEQ ID NO: 1) or fragments thereof, which, in certain embodiments, are consecutive with the amino acid residues of ICP4.2 being used. Exemplary fragments that combine the residues of SEQ ID NO: 2 with select residues from 1-382 or 767-1318 of SEQ ID NO: 1 are described above.

[0116] An immunogenic fragment of ICP4.2 comprises at least one immunogenic portion, as measured experimentally or identified by algorithm. Peptides identified by such methods include the following:

GLAHVAAAV (SEQ ID NO: 47)

FISGSVARA (SEQ ID NO: 48)

QYALITRLL (SEQ ID NO: 49)

RYDRAQKGF (SEQ ID NO: 50)

GYAMAAGRF (SEQ ID NO: 51)

PPHADAPRL (SEQ ID NO: 52)

KPAAAAAPL (SEQ ID NO: 53)

SEAAVAAV (SEQ ID NO: 54)

FGWGLAHV (SEQ ID NO: 55)

YALITRLLY (SEQ ID NO: 56)

ALPRSPRLL (SEQ ID NO: 57)

DLLFQNQSL (SEQ ID NO: 58)

ADLLFQNQS (SEQ ID NO: 59)

ARNSSSFIS (SEQ ID NO: 60)

QACFRISGA (SEQ ID NO: 61)

FVRDALVLM (SEQ ID NO: 62)

FDGDLAAVP (SEQ ID NO: 63)

GLGDSRPGL (SEQ ID NO: 64)

WAPELGDAA (SEQ ID NO: 65)

ECLAACRGI (SEQ ID NO: 66)

RAWLRELRF (SEQ ID NO: 67).

[0117] Thus, in some aspects, this disclosure provides an immunogenic fragment of ICP4.2. The fragments, in some instances, are close in size to the full-length polypeptide. For example, they may lack at most one, two, three, four, five, ten, or twenty amino acids from one or both termini. In other embodiments, the fragment is 100-391 amino acids in length, or 150-391, or 200-391, or 250-391 amino acids in length. Other exemplary fragments are amino acid residues 1-350, 1-300, 1-250, 1-200, 1-150, 1-100, 1-50, 50-391, 50-350, 50-300, 50-250, 50-200, 50-150, 50-100 , 100-391, 100-350, 100-300, 100-250, 100-200, 100-150, 150-391, 150-350, 150-300, 150-250, 150-200, 200-391, 200-350, 200-300, 200-250, 250-391, 250-350, 250-300, 300-391 and 350-391. The fragments described above or sub-fragments thereof (*e.g.*, fragments of 8-50, 8-30, or 8-20 amino acid residues) preferably have one of the biological activities described below, such as increasing the T cell response by at least 1.5 fold or 2 fold. A fragment may be used as the polypeptide in the vaccines described herein or may be fused to another protein, protein fragment or a polypeptide.

[0118] In certain aspects, this application provides immunogenic polypeptides with at least 90%, 95%, 97%, 98%, 99%, or 99.5% identity to ICP4.2 or an immunogenic fragment thereof.

Glycoprotein L-2 (SEQ ID NO: 3 or SEQ ID NO: 136) encoded by UL1

[0119] UL1 encodes Glycoprotein L-2 (gL2), a heterodimer glycoprotein that is required for the fusion of viral and cellular membranes and enables the virus to enter the host cell. The DNA and protein sequence of UL1 may be found by searching in the publicly available database, Entrez Gene (on the NCBI NIH web site on the World Wide Web, at ww.ncbi.nlm.nih.gov/sites/entrez?db=gene), in the Human herpesvirus 2 complete genome.

[0120] In some embodiments, the polypeptide may be a cytoplasmic form of UL1 (SEQ ID NO:3). In other embodiments, the polypeptide may be a secreted form of UL1, which lacks one or more amino acids of the signal sequence. An exemplary polypeptide of the secreted form of UL1 is the polypeptide of SEQ ID NO: 136. In certain embodiments, this polypeptide will not form an aggregate after it is substantially purified. In some embodiments, the polypeptide will

contain one or more amino acids corresponding to a signal sequence that has been cleaved. The signal sequence may be a mammalian signal sequence or may be a non-mammalian signal sequence, depending on the system from which the polypeptide was purified.

[0121] In some embodiments, an immunogenic composition described herein includesa polypeptide containing at least 20 consecutive amino acid residues selected from residues 1-224 or 1-200 of gL2 (SEQ ID NO: 3 or SEQ ID NO: 136), but no more than 224 or 200 amino acids of gL2 (SEQ ID NO: 3 or SEQ ID NO: 136). The polypeptide may also be a variant of the at least 20 residue fragment.

[0122] In some embodiments, the polypeptide is at least 85% identical to a fragment of 150-200 or 200-250 amino acids of SEQ ID NO: 3 or SEQ ID NO: 136.

[0123] In certain embodiments, the polypeptide includes no more than 200 or 100 consecutive amino acids from gL2. Exemplary polypeptides are amino acids residues 1-20, 21-40, 41-60, of 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-221 of gL2 (SEQ ID NO: 3 or amino acids residues 1-20, 21-40, 41-60, of 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, or 181-200 SEQ ID NO: 136) and the like.

[0124] In other aspects, the disclosure provides an immunogenic fragment of gL2. An immunogenic fragment of gL2 comprises at least one immunogenic portion, as measured experimentally or identified by algorithm. Peptides identified by such methods include the following:

AYLVNPFLF (SEQ ID NO: 100)

PFLFAAGFL (SEQ ID NO: 101)

TEYVLRSVI (SEQ ID NO: 102)

GSQATEYVL (SEQ ID NO: 103)

RIDGIFLRY (SEQ ID NO: 104)

FLEDLSHSV (SEQ ID NO: 105)

YVLRSVIAK (SEQ ID NO: 106)

YVLRSVIAK (SEQ ID NO: 107)

AYLVNPFLF (SEQ ID NO: 108)

ETTTRRALY (SEQ ID NO: 109)

RIDGIFLRY (SEQ ID NO: 110)

YLVNPFLFA (SEQ ID NO: 111)

FVCLFGLVV (SEQ ID NO: 112)

LYKEIRDAL (SEQ ID NO: 113)

GLDTFLWDR (SEQ ID NO: 114)

RVSPTRGRR (SEQ ID NO: 115)

YVLRSVIAK (SEQ ID NO: 142)

GLDTFLWDR (SEQ ID NO: 116)

DILRVPCMR (SEQ ID NO: 143)

DRHAQRAYL (SEQ ID NO: 144)

Glycoprotein D-2 (SEQ ID NO: 5) encoded by US6 and internally-deleted Glycoprotein D-2 (SEQ ID NO: 4) encoded by US6ΔTMR

[0125] US6 encodes envelope glycoprotein D-2 (gD2), an envelope glycoprotein that binds to host cell entry receptors and may trigger fusion of the virus with the host membrane. The gD2 protein has several distinct domains, including a signal domain (amino acid residues 1-25) which is cleaved from the mature protein, and a transmembrane domain (spanning

approximately amino acids residues 340-363). The DNA and protein sequence of US6 may be found by searching in the publicly available database, Entrez Gene (on the NCBI NIH web site on the World Wide Web, at www.ncbi.nlm.nih.gov/sites/entrez?db=gene), in the Human herpesvirus 2 complete genome.

[0126] In some embodiments, an immunogenic composition described herein includesa polypeptide comprising gD2 that is missing all or part of the transmembrane domain (which spans approximately amino acids residues 340-363 inclusive) as well as the signal sequence. In other embodiments, the deleted region may additionally include 5-10 amino acids of the sequence flanking the transmembrane domain. The deleted region may also comprise a portion of the transmembrane domain, for example at least 3 amino acids between residues 340-363. In some embodiments, at least one residue in the transmembrane domain has been modified, deleted or substituted, such that the transmembrane domain is no longer functional. For example, a variant may have its internal deletion begin at amino acid residue 336, 337, 338, 339, 340, 341, 342, 343, 344, 345 or 346 and end at amino acid residue 358, 359, 360, 361, 362, 363, 364, 365, 366, 367 or 368.

[0127] A construct encoding gD2 which is missing amino acid residues 340-363 (the transmembrane domain) is called US6ΔTMR (SEQ ID NO: 40). The corresponding protein is denoted gD2ΔTMR (SEQ ID NO: 4). In other embodiments, an immunogenic fragment of gD2 or gD2ΔTMR may comprise a deletion in a portion of the transmembrane domain, and/or may comprise a deletion in the flanking sequence outside of the transmembrane domain.

[0128] In other aspects, the disclosure provides an immunogenic fragment of gD2 or gD2ΔTMR. An immunogenic fragment of gD2 or gD2ΔTMR comprises at least one immunogenic portion, as measured experimentally or identified by algorithm. Peptides identified by such methods include the following:

ALAGSTLAV (SEQ ID NO: 68)

LLEDPAGTV (SEQ ID NO: 69)

VIGGIAFWV (SEQ ID NO: 70)

TVYYAVLER (SEQ ID NO: 71)

KYALADPSL (SEQ ID NO: 72)

AFETAGTYL (SEQ ID NO: 73)

APSNPGLII (SEQ ID NO: 74)

IPITVYYAV (SEQ ID NO: 75)

APPSHQPLF (SEQ ID NO: 76)

FLMHAPAFE (SEQ ID NO: 77)

FSAVSEDNL (SEQ ID NO: 78)

VYYAVLER (SEQ ID NO: 79)

IGMLPRFI (SEQ ID NO: 80)

YTECPYNKS (SEQ ID NO: 81)

FLMHAPAFE (SEQ ID NO: 82)

NLGFLMHAP (SEQ ID NO: 83)

VIGGIAFWV (SEQ ID NO: 84)

GIAFWVRRR (SEQ ID NO: 85)

SEDNLGFLM (SEQ ID NO: 86)

RTQPRWSYY (SEQ ID NO: 87)

IAFWVRRRA (SEQ ID NO: 88)

LVIGGIAFW (SEQ ID NO: 89)

FWVRRRAQM (SEQ ID NO: 90)

PYTSTLLPP (SEQ ID NO: 91)

VGTAALLVV (SEQ ID NO: 92)

TAALLVVAV (SEQ ID NO: 93)

TSTLLPPEL (SEQ ID NO: 94)

GTVSSQIPP (SEQ ID NO: 95)

TAGTYLRLV (SEQ ID NO: 96)

GVTVDSIGM (SEQ ID NO: 97)

AFWVRRRAQ (SEQ ID NO: 98)

RVYHIQPSL (SEQ ID NO: 99)

[0129] Thus, in some aspects, the disclosure provides an immunogenic fragment of gD2 (SEQ ID NO: 5) or gD2ΔTMR (SEQ ID NO: 4). The fragments, in some instances, are close in size to the full-length polypeptide. For example, they may lack at most one, two, three, four, five, ten, or twenty amino acids from one or both termini. In other embodiments, the fragment is 100-393 amino acids in length, or 150-393, or 200-393, or 250-393 amino acids in length. Other exemplary fragments are amino acid residues 1-350, 1-300, 1-250, 1-200, 1-150, 1-100, 1-50, 50-393, 50-350, 50-300, 50-250, 50-200, 50-150, 50-100, 100-393, 100-350, 100-300, 100-250, 100-200, 100-150, 150-393, 150-350, 150-300, 150-250, 150-200, 200-393, 200-350, 200-300, 200-250, 250-393, 250-350, 250-300, 300-393 and 350-393. The fragments described above or sub-fragments thereof (*e.g.*, fragments of 8-50, 8-30, or 8-20 amino acid residues) preferably have one of the biological activities described below, such as increasing the T cell response by at least 1.5 fold or 2 fold. A fragment may be used as the polypeptide in the vaccines described herein or may be fused to another protein, protein fragment or a polypeptide.

[0130] In other embodiments, the polypeptide comprises the entire sequence of SEQ ID NO: 4 or SEQ ID NO: 5, or consists of the entire sequence of SEQ ID NO: 4 or SEQ ID NO: 5. In certain embodiments, an immunogenic fragment of gD2 retains all or part of the signal domain (amino acid residues 1-25) and/or the transmembrane domain (amino acids residues 340-363).

[0131] In certain embodiments, polypeptides have less than 20%, 30%, 40%, 50%, 60% or 70% homology with human autoantigens. Examples of such autoantigens include UL6 from HSV-1 and gK or UL53 from HSV-2.

[0132] In certain aspects, this application provides immunogenic polypeptides with at least 90%, 95%, 97%, 98%, 99%, or 99.5% identity to gD2ΔTMR, or an immunogenic fragment thereof.

ICP4 internal fragment ICP4.5 (SEQ ID NO: 13) encoded by RS1.5

[0133] RS1.5 encodes a 544 amino acid fragment corresponding to residues 775-1318 of ICP4, denoted ICP4.5. The DNA and protein sequences of RS1.5 may be found by searching for RS1 in the publicly available database, Entrez Gene (on the NCBI NIH web site on the World Wide Web, at www.ncbi.nlm.nih.gov/sites/entrez?db=gene), in the Human herpes virus 2 complete genome.

[0134] In specific embodiments, an immunogenic composition described herein includesa polypeptide containing from 50 to all 544 amino acids residues of ICP4.5 (SEQ ID NO: 13), such as 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 544 residues. In particular embodiments, the polypeptide includes all of ICP4.5 (SEQ ID NO: 13) or is ICP4.5 (SEQ ID NO: 13) itself. These polypeptides may, for example, include the full length or fragments of ICP4.5 (SEQ ID NO: 13) described herein with amino acid residues 1-774 of ICP4 (SEQ ID NO: 1) or fragments thereof, which, in certain embodiments, are consecutive with the amino acid residues of ICP4.5 being used. Exemplary fragments that combine the residues of SEQ ID NO: 13 with select residues from 1-774 of SEQ ID NO: 1 are described above.

[0135] An immunogenic fragment of ICP4.5 comprises at least one immunogenic portion, as measured experimentally or identified by algorithm. Thus, in some aspects, this application provides an immunogenic fragment of ICP4.5. The fragments, in some instances, are close in size to the full-length polypeptide. For example, they may lack at most one, two, three, four, five, ten, or twenty amino acids from one or both termini. In other embodiments, the fragment is 50-544 amino acids in length, or 100-544, or 150-544, or 200-544, or 250-544, or 300-544, or 350-544, or 400-544, or 450-544, or 500-544 amino acids in length. Other exemplary fragments are amino acid residues 1-500, 1-450, 1-400, 1-350, 1-300, 1-250, 1-200, 1-150, 1-100, 1-50, 50-544, 50-500, 50-450, 50-400, 50-350, 50-300, 50-250, 50-200, 50-150, 50-100, 100-544, 100-500, 100-450, 100-400, 100-350, 100-300, 100-250, 100-200, 100-150, 150-544, 150-500, 150-450, 150-400, 150-350, 150-300, 150-250, 150-200, 200-544, 200-500, 200-450, 200-400, 200-350, 200-300, 200-250, and so forth. The fragments described above or sub-fragments thereof (*e.g.*, fragments of 8-50, 8-30, or 8-20 amino acid residues) preferably have one of the biological activities described below, such as increasing the T cell response by at least 1.5 fold or 2 fold. A fragment may be used as the polypeptide in the vaccines described herein or may be fused to another protein, protein fragment or a polypeptide.

[0136] In certain aspects, the disclosure provides immunogenic polypeptides with at least 90%, 95%, 97%, 98%, 99%, or 99.5% identity to ICP4.5 or an immunogenic fragment thereof.

ICP4 fragment ICP4.9 (SEQ ID NO: 138) encoded by RS1.9, and ICP4 fragment ICP4.10 (SEQ ID NO: 139) encoded by RS1.10

[0137] RS1.9 encodes a 1130 amino acid fragment of ICP4, carrying a double internal deletion of residues 391-544 and residues 786-821 of ICP4, denoted ICP4.9. RS1.10 encodes a 1166 amino acid fragment of ICP4, carrying a double internal deletion of residues 391-508 and residues 786-821 of ICP4, denoted ICP4.10. The DNA and protein sequences of RS1.9 and RS1.10 may be found by searching for RS1 in the publicly available database, Entrez Gene (on the NCBI NIH web site on the World Wide Web, at www.ncbi.nlm.nih.gov/sites/entrez?db=gene), in the Human herpesvirus 2 complete genome.

[0138] In specific embodiments, an immunogenic composition described herein includesa polypeptide containing from 50 to all 1130 or 1166 amino acids residues of ICP4.9 (SEQ ID NO: 138) or ICP4.10 (SEQ ID NO: 139), such as 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1130 or 1166 residues. In particular embodiments, the polypeptide includes all of ICP4.9 (SEQ ID NO: 138) or ICP4.10 (SEQ ID NO: 139), or is ICP4.9 (SEQ ID NO: 138) or ICP4.10 (SEQ ID NO: 139) itself. These polypeptides may, for example, include the full length or fragments of ICP4.9 (SEQ ID NO: 138) or ICP4.10 (SEQ ID NO: 139) described herein.

[0139] An immunogenic fragment of ICP4.9 or ICP4.10 comprises at least one immunogenic portion, as measured experimentally or identified by algorithm. Thus, in some aspects, this application provides an immunogenic fragment of ICP4.9 or ICP4.10. The fragments, in some instances, are close in size to the full-length polypeptide. For example, they may lack at most one, two, three, four, five, ten, or twenty amino acids from one or both termini. In other embodiments, the fragment is 50-1130 amino acids in length, or 100-1130, 150-1130, or 200-1130, or 250-1130, or 300-1130, or 400-1130, or 500-1130, or 600-1130, or 700-1130, or 800-1130, or 900-1130, or 1000-1130 amino acids in length. Other exemplary fragments are amino acid residues 1-1130, 1-1000, 1-900, 1-800, 1-700, 1-600, 1-500, 1-400, 1-300, 1-200, 1-150, 1-100, 1-50, 50-1130, 50-1000, 50-900, 50-800, 50-700, 50-600, 50-500, 50-400, 50-300, 50-250, 50-200, 50-150, 50-100, 100-1130, 100-1000, 100-900, 100-800, 100-700, 100-600, 100-500, 100-400, 100-300, 100-250, 100-200, 100-150, and so forth. The fragments described above or sub-fragments thereof (*e.g.*, fragments of 8-50, 8-30, or 8-20 amino acid residues) preferably have one of the biological activities described below, such as increasing the T cell response by at least 1.5 fold or 2 fold. A fragment may be used as the polypeptide in the vaccines described herein or may be fused to another protein, protein fragment or a polypeptide.

[0140] In certain embodiments, an analog of ICP4.9 is based on SEQ ID NO: 1, where at least 50, 75, 100, 125, 130, 140, 145 or 150 residues from residues 391-544 are deleted. Separately or in combination, at least 20, 25, or 30 residues from residues 786-821 are deleted.

[0141] In certain embodiments, an analog of ICP4.10 is based on SEQ ID NO: 1, where at least 25, 50, 75, 90, 95, 100, 105, 110 or 115 residues from residues 391-508 are deleted.

Separately or in combination, at least 25, 50, 60, 65, 70 or 75 residues from residues 786-821 are deleted.

[0142] In certain aspects, the disclosure provides immunogenic polypeptides with at least 90%, 95%, 97%, 98%, 99%, or 99.5% identity to ICP4.9 or ICP4.10, or an immunogenic fragment or analog thereof.

Additional features of HSV-2 polypeptides

[0143] Typically, the polypeptides present in an immunogenic composition described herein are immunogenic, either alone or as a variant, which includes polypeptides fused to another polypeptide or mixed with or complexed to an adjuvant. Variants also include sequences with less than 100% sequence identity, as described herein. In addition, one may use fragments, precursors and analogs that have an appropriate immunogenicity.

[0144] These polypeptides may be immunogenic in mammals, for example, mice, guinea pigs, or humans. An immunogenic polypeptide is typically one capable of raising a significant immune response in an assay or in a subject. Alternatively, an immunogenic polypeptide may (i) induce production of antibodies, *e.g.*, neutralizing antibodies, that bind to the polypeptide (ii) induce T_H1 immunity, (iii) activate the $CD8^+$ T cell response, for example by increasing the number of $CD8^+$ T cells, increasing localization of $CD8^+$ T cells to the site of infection or reinfection, , (iv) induce T_H17 immunity, and/or (v) activate innate immunity. In some embodiments, an immunogenic polypeptide causes the production of a detectable amount of antibody specific to that antigen.

[0145] In certain embodiments, polypeptides have less than 20%, 30%, 40%, 50%, 60% or 70% homology with human autoantigens.

[0146] A polypeptide may comprise one or more immunogenic portions and one or more non-immunogenic portions. The immunogenic portions may be identified by various methods, including protein microarrays, ELISPOT/ELISA techniques, and/or specific assays on different deletion mutants (*e.g.*, fragments) of the polypeptide in question. Immunogenic portions may

also be identified by computer algorithms. Some such algorithms, like EpiMatrix (produced by EpiVax), use a computational matrix approach. Other computational tools for identifying antigenic epitopes include PEPVAC (Promiscuous EPitope-based VACcine, hosted by Dana Farber Cancer Institute on the world wide web at immunax.dfci.harvard.edu/PEPVAC), MHCPred (which uses a partial least squares approach and is hosted by The Jenner Institute on the world wide web at www.jenner.ac.uk/MHCPred), and Syfpeithi, hosted on the world wide web at www.syfpeithi.de/.

[0147] In some embodiments, an immunogenic composition described herein may comprise fusion proteins and/or fusion DNA constructs. The underlying DNA sequences above may be modified in ways that do not affect the sequence of the protein product. For instance, the DNA sequence may be codon-optimized to improve expression in a host such as *E. coli* or an insect cell line (*e.g.*, using the baculovirus expression system) or mammalian (*e.g.*, Chinese Hamster Ovary) cell line. In certain embodiments, the DNA sequence may comprise an exogenous sequence, such as an exogenous signal sequence, for expression in non-mammalian cells. In particular embodiments, such as when smaller related polypeptides, including those having a molecular weight less than about 5000 daltons, *e.g.*, 1500 to 5000 daltons, are used, modification may be useful in eliciting the desired immune response. For example, the smaller polypeptides can be conjugated to an appropriate immunogenic carrier such as proteins from other pathogenic organisms or viruses (*e.g.*, tetanus toxoid), large proteins (*e.g.*, keyhole limpet hemocyanin) or the like. Conjugation may be direct or indirect (*e.g.*, via a linker). In other particular embodiments, a fusion protein may comprise a polypeptide disclosed above or an immunogenic fragment or variant thereof and a tag. A tag may be N-terminal or C-terminal. For instance, tags may be added to the nucleic acid or polypeptide to facilitate purification, detection, solubility, or confer other desirable characteristics on the protein or nucleic acid. For instance, a purification tag may be a peptide, oligopeptide, or polypeptide that may be used in affinity purification. Examples include His, GST, TAP, FLAG, myc, HA, MBP, VSV-G, thioredoxin, V5, avidin, streptavidin, BCCP, Calmodulin, Nus, S tags, lipoprotein D, and β galactosidase. In some embodiments, the fused portion is short. Thus, in some instances, the fusion protein comprises no more than 1, 2, 3, 4, 5, 10, 20, or 50 additional amino acids on one or both termini

of a polypeptide described above, such as consecutive amino acids from any of the polypeptides in Table 1.

[0148] In some embodiments, tags, secretion signals, or other signal sequences may be added to the C-terminal end and/or to the N-terminal end of the polypeptide. Tags may be used to aid in purification of expresssed polypeptides. Exemplary tags include HHHHHH (SEQ ID NO: 130) and MSYYHHHHHH (SEQ ID NO: 131). Secretion signals may be optimized for use with non-mammalian cells, such as insect cells. An exemplary secretion signal is MKFLVNVALVFMVVYISYIYA (SEQ ID NO: 132).

[0149] A detection tag may be used to detect the tag and, consequently, any amino acid sequence fused to it. Detection tags include fluorescent proteins, proteins that bind a fluorescent label, and proteins that bind an electron-dense moeity. Examples of fluorescent proteins include dsRed, mRFP, YFP, GFP, CFP, BFP, and Venus. An example of a protein that binds a fluorescent or electron-dense label is FlAsH.

[0150] Another aspect disclosed herein is an antibody preparation generated against a composition of the invention (*e.g.*, a composition comprising one or more, or two or more of the polypeptides listed in Table 1). Any of a variety of antibodies are included. Such antibodies include, *e.g.*, polyclonal, monoclonal, recombinant, humanized or partially humanized, single chain, Fab, and fragments thereof, etc. The antibodies can be of any isotype, *e.g.*, IgA, IgG, various IgG isotypes such as IgG_1, IgG_2, IgG_{2a}, IgG_{2b}, IgG_3, IgG_4, etc.; and they can be from any animal species that produces antibodies, including goat, rabbit, mouse, chicken or the like. In some embodiments, Fab molecules are expressed and assembled in a genetically transformed host like *E. coli*. A lambda vector system is available thus to express a population of Fab's with a potential diversity equal to or exceeding that of the subject generating the predecessor antibody. See Huse *et al.* (1989), Science 246, 1275-81.

Components of immunogenic and pharmaceutical compositions

[0151] In certain embodiments, an immunogenic composition e.g., a vaccine, vaccine formulation, and/or a pharmaceutical composition described herein, comprises one or more of

the polypeptides and nucleic acids described above and one or more of the following: an adjuvant, stabilizer, buffer, surfactant, controlled-release component, salt, preservative, and an antibody specific to said antigen.

Adjuvants

[0152] Immunogenic compositions described herein may include an adjuvant. Adjuvants can be broadly separated into two classes, based on their principal mechanisms of action: vaccine delivery systems and immunostimulatory adjuvants (see, *e.g.*, Singh *et al.*, *Curr. HIV Res.* 1:309-20, 2003). Vaccine delivery systems are often particulate formulations, *e.g.*, emulsions, microparticles, immune-stimulating complexes (ISCOMs), which may be, for example, particles and/or matrices, and liposomes. In contrast, immunostimulatory adjuvants are sometimes derived from pathogens and can represent pathogen associated molecular patterns (PAMP), *e.g.*, lipopolysaccharides (LPS), monophosphoryl lipid (MPL), or CpG-containing DNA, which activate cells of the innate immune system.

[0153] Alternatively, adjuvants may be classified as organic and inorganic. Inorganic adjuvants include aluminum salts such as aluminum phosphate, amorphous aluminum hydroxyphosphate sulfate, and aluminum hydroxide, which are commonly used in human vaccines. Organic adjuvants comprise organic molecules including macromolecules. An example of an organic adjuvant is cholera toxin.

[0154] Adjuvants may also be classified by the response they induce, and adjuvants can activate more than one type of response. In some embodiments, the adjuvant induces the activation of $CD4^+$ T cells. The adjuvant may induce activation of T_H1 cells and/or activation of T_H17 cells and/or activation of T_H2 cells. Alternately, the adjuvant may induce activation of T_H1 cells and/or T_H17 cells but not activation of T_H2 cells, or vice versa. In some embodiments, the adjuvant induces activation of $CD8^+$T cells. In further embodiments, the adjuvant may induce activation of Natural Killer T (NKT) cells. In some embodiments, the adjuvant induces the activation of T_H1 cells or T_H17 cells or T_H2 cells. In other embodiments, the adjuvant induces the activation of B cells. In yet other embodiments, the adjuvant induces the activation of APCs.

These categories are not mutually exclusive; in some cases, an adjuvant activates more than one type of cell.

[0155] In certain embodiments, an adjuvant is a substance that increases the numbers or activity of APCs such as dendritic cells. In certain embodiments, an adjuvant promotes the maturation of APCs such as dendritic cells. In some embodiments, the adjuvant is or comprises a saponin. Typically, the saponin is a triterpene glycoside, such as those isolated from the bark of the *Quillaja saponaria* tree. A saponin extract from a biological source can be further fractionated (*e.g.*, by chromatography) to isolate the portions of the extract with the best adjuvant activity and with acceptable toxicity. Typical fractions of extract from *Quillaja saponaria* tree used as adjuvants are known as fractions A and C. An exemplary saponin adjuvant is QS-21 (fraction C), which is available from Antigenics. QS-21 is an oligosaccharide-conjugated small molecule. Optionally, QS-21 may be admixed with a lipid such as 3D-MPL or cholesterol.

[0156] A particular form of saponins that may be used in vaccine formulations described herein is immunostimulating complexes (ISCOMs). ISCOMs are an art-recognized class of adjuvants, that generally comprise *Quillaja* saponin fractions and lipids (*e.g.*, cholesterol and phospholipids such as phosphatidyl choline). In certain embodiments, an ISCOM is assembled together with a polypeptide or nucleic acid of interest. However, different saponin fractions may be used in different ratios. In addition, the different saponin fractions may either exist together in the same particles or have substantially only one fraction per particle (such that the indicated ratio of fractions A and C are generated by mixing together particles with the different fractions). In this context, "substantially" refers to less than 20%, 15%, 10%, 5%, 4%, 3%, 2% or even 1%. Such adjuvants may comprise fraction A and fraction C mixed into a ratio of 70-95 A: 30-5 C, such as 70 A : 30 C to 75 A : 25 C; 75 A : 25 C to 80 A : 20 C; 80 A : 20 C to 85 A : 15 C; 85 A : 15 C to 90 A : 10 C; 90 A : 10 C to 95 A : 5 C; or 95 A : 5 C to 99 A : 1 C. ISCOMatrix, produced by CSL, and AbISCO 100 and 300, produced by Isconova, are ISCOM matrices comprising saponin, cholesterol and phospholipid (lipids from cell membranes), which form cage-like structures typically 40-50 nm in diameter. Posintro, produced by Nordic Vaccines, is an ISCOM matrix where the immunogen is bound to the particle by a multitude of different

mechanisms, *e.g.,* electrostatic interaction by charge modification, incorporation of chelating groups, or direct binding.

[0157] In some embodiments, the adjuvant is a TLR ligand. TLRs are proteins that may be found on leukocyte membranes, and recognize foreign antigens (including microbial antigens). An exemplary TLR ligand is IC-31, which is available from Intercell. IC-31 comprises an anti-microbial peptide, KLK, and an immunostimulatory oligodeoxynucleotide, ODN1a. IC-31 has TLR9 agonist activity. Another example is CpG-containing DNA. Different varieties of CpG-containing DNA are available from Prizer (Coley): VaxImmune is CpG 7909 (a (CpG)-containing oligodeoxy-nucleotide), and Actilon is CpG 10101 (a (CpG)-containing oligodeoxy-nucleotide).

[0158] In some embodiments, the adjuvant is a nanoemulsion. One exemplary nanoemulsion adjuvant is Nanostat Vaccine, produced by Nanobio. This nanoemulsion is a high-energy, oil-in-water emulsion. This nanoemulsion typically has a size of 150-400 nanometers, and includes surfactants to provide stability. More information about Nanostat can be found in US Patents 6,015,832, 6,506,803, 6,559,189, 6,635,676, and 7,314,624.

[0159] In some embodiments, an adjuvant includes a cytokine. In some embodiments, the cytokine is an interleukin such as IL-1, IL-6, IL-12, IL-17 and IL-23. In some embodiments, the cytokine is granulocyte-macrophage colony-stimulating factor (GM-CSF). The adjuvant may include cytokine as a purified polypeptide. Alternatively, the adjuvant may include nucleic acids encoding the cytokine.

[0160] Adjuvants may be covalently bound to antigens (*e.g.*, the polypeptides described above). In some embodiments, the adjuvant may be a protein which induces inflammatory responses through activation of APCs. In some embodiments, one or more of these proteins can be recombinantly fused with an antigen of choice, such that the resultant fusion molecule promotes dendritic cell maturation, activates dendritic cells to produce cytokines and chemokines, and ultimately, enhances presentation of the antigen to T cells and initiation of T cell responses (see Wu *et al.*, Cancer Res 2005; 65(11), pp 4947-4954). Other exemplary

adjuvants that may be covalently bound to antigens comprise polysaccharides, synthetic peptides, lipopeptides, and nucleic acids.

[0161] The adjuvant can be used alone or in combination of two or more kinds. Adjuvants may be directly conjugated to antigens. Adjuvants may also be combined to increase the magnitude of the immune response to the antigen. Typically, the same adjuvant or mixture of adjuvants is present in each dose of a vaccine. Optionally, however, an adjuvant may be administered with a first dose of vaccine and not with subsequent doses (e.g., booster shots). Alternatively, a strong adjuvant may be administered with the first dose of vaccine and a weaker adjuvant or lower dose of the strong adjuvant may be administered with subsequent doses. The adjuvant can be administered before the administration of the antigen, concurrent with the administration of the antigen or after the administration of the antigen to a subject (sometimes within 1, 2, 6, or 12 hours, and sometimes within 1, 2, or 5 days). Certain adjuvants are appropriate for human patients, non-human animals, or both.

Additional components of immunogenic and pharmaceutical compositions

[0162] In addition to the antigens and the adjuvants described above, an immunogenic composition, e.g., a vaccine, a vaccine formulation and/or a pharmaceutical composition, may include one or more additional components.

[0163] In certain embodiments, an immunogenic composition may include one or more stabilizers such as sugars (such as sucrose, glucose, or fructose), phosphate (such as sodium phosphate dibasic, potassium phosphate monobasic, dibasic potassium phosphate, or monosodium phosphate), glutamate (such as monosodium L-glutamate), gelatin (such as processed gelatin, hydrolyzed gelatin, or porcine gelatin), amino acids (such as arginine, asparagine, histidine, L-histidine, alanine, valine, leucine, isoleucine, serine, threonine, lysine, phenylalanine, tyrosine, and the alkyl esters thereof), inosine, or sodium borate.

[0164] In certain embodiments, an immunogenic composition includes one or more buffers such as a mixture of sodium bicarbonate and ascorbic acid. In some embodiments, an immunogenic composition may be administered in saline, such as phosphate buffered saline (PBS), or distilled water.

[0165] In certain embodiments, an immunogenic composition includes one or more surfactants such as polysorbate 80 (Tween 80), Polyethylene glycol tert-octylphenyl ether t-Octylphenoxypolyethoxyethanol 4-(1,1,3,3-Tetramethylbutyl)phenyl-polyethylene glycol (TRITON X-100); Polyoxyethylenesorbitan monolaurate Polyethylene glycol sorbitan monolaurate (TWEEN 20); and 4-(1,1,3,3-Tetramethylbutyl)phenol polymer with formaldehyde and oxirane (TYLOXAPOL). A surfactant can be ionic or nonionic.

[0166] In certain embodiments, an immunogenic composition includes one or more salts such as sodium chloride, ammonium chloride, calcium chloride, or potassium chloride.

[0167] In certain embodiments, a preservative is included in an immunogenic composition. In other embodiments, no preservative is used. A preservative is most often used in multi-dose vaccine vials, and is less often needed in single-dose vaccine vials. In certain embodiments, the preservative is 2-phenoxyethanol, methyl and propyl parabens, benzyl alcohol, and/or sorbic acid.

[0168] In certain embodiments, an immunogenic composition is a controlled-release formulation.

DNA immunogenic compositions

[0169] In certain aspects, an immunogenic composition, e.g., a vaccine, a vaccine formulation and/or a pharmaceutical composition, comprises one or more of the nucleic acids disclosed herein. When a nucleic acid vaccine is administered to a patient, the corresponding gene product (such as a desired antigen) is produced in the patient's body. In some embodiments, nucleic acid vaccine vectors that include optimized recombinant polynucleotides can be delivered to a mammal (including humans) to induce a therapeutic or prophylactic immune response. The nucleic acid may be, for example, DNA, RNA, or a synthetic nucleic acid. The nucleic acid may be single stranded or double-stranded.

[0170] Nucleic acid vaccine vectors (*e.g.*, adenoviruses, liposomes, papillomaviruses, retroviruses, etc.) can be administered directly to the mammal for transduction of cells *in vivo*.

The nucleic acid vaccines can be formulated as pharmaceutical compositions for administration in any suitable manner, including parenteral administration. Plasmid vectors are typically more efficient for gene transfer to muscle tissue. The potential to deliver DNA vectors to mucosal surfaces by oral administration has also been reported (PLGA encapsulated Rotavirus and Hepatitis B) and DNA plasmids have been utilized for direct introduction of genes into other tissues. DNA vaccines have been introduced into animals primarily by intramuscular injection, by gene gun delivery, or by electroporation. After being introduced, the plasmids are generally maintained episomally without replication. Expression of the encoded proteins has been shown to persist for extended time periods, providing stimulation of B and T cells.

[0171] In determining the effective amount of the vector to be administered in the treatment or prophylaxis of an infection or other condition, the physician evaluates vector toxicities, progression of the disease, and the production of anti-vector antibodies, if any. Often, the dose equivalent of a naked nucleic acid from a vector is from about 1 μg to 1 mg for a typical 70 kilogram patient, and doses of vectors used to deliver the nucleic acid are calculated to yield an equivalent amount of therapeutic nucleic acid. Administration can be accomplished via single or divided doses. The toxicity and therapeutic efficacy of the nucleic acid vaccine vectors can be determined using standard pharmaceutical procedures in cell cultures or experimental animals.

[0172] A nucleic acid vaccine can contain DNA, RNA, a modified nucleic acid, or a combination thereof. In some embodiments, the vaccine comprises one or more cloning or expression vectors; for instance, the vaccine may comprise a plurality of expression vectors each capable of autonomous expression of a nucleotide coding region in a mammalian cell to produce at least one immunogenic polypeptide. An expression vector often includes a eukaryotic promoter sequence, such as the nucleotide sequence of a strong eukaryotic promoter, operably linked to one or more coding regions. The compositions and methods herein may involve the use of any particular eukaryotic promoter, and a wide variety are known, such as a CMV or RSV promoter. The promoter can be, but need not be, heterologous with respect to the host cell. The promoter used may be a constitutive promoter.

[0173] A vector useful in the present compositions and methods can be circular or linear, single-stranded or double stranded and can be a plasmid, cosmid, or episome. In a suitable

embodiment, each nucleotide coding region is on a separate vector; however, it is to be understood that one or more coding regions can be present on a single vector, and these coding regions can be under the control of a single or multiple promoters.

[0174] Numerous plasmids may be used for the production of nucleic acid vaccines. Suitable embodiments of the nucleic acid vaccine employ constructs using the plasmids VR1012 (Vical Inc., San Diego Calif.), pCMVI.UBF3/2 (S. Johnston, University of Texas) or pcDNA3.1 (InVitrogen Corporation, Carlsbad, Calif.) as the vector. In addition, the vector construct can contain immunostimulatory sequences (ISS), such as unmethylated dCpG motifs, that stimulate the animal's immune system. The nucleic acid vaccine can also encode a fusion product containing the immunogenic polypeptide. Plasmid DNA can also be delivered using attenuated bacteria as delivery system, a method that is suitable for DNA vaccines that are administered orally. Bacteria are transformed with an independently replicating plasmid, which becomes released into the host cell cytoplasm following the death of the attenuated bacterium in the host cell.

[0175] DNA vaccines, including the DNA encoding the desired antigen, can be introduced into a host cell in any suitable form including, the fragment alone, a linearized plasmid, a circular plasmid, a plasmid capable of replication, an episome, RNA, etc. Preferably, the gene is contained in a plasmid. In certain embodiments, the plasmid is an expression vector. Individual expression vectors capable of expressing the genetic material can be produced using standard recombinant techniques. See e.g., Maniatis et al., 1985 Molecular Cloning: A Laboratory Manual or DNA Cloning, Vol. I and II (D. N. Glover, ed., 1985) for general cloning methods.

[0176] Routes of administration include, but are not limited to, intramuscular, intranasal, intraperitoneal, intradermal, subcutaneous, intravenous, intraarterially, intraoccularly and oral as well as topically, transdermally, by inhalation or suppository or to mucosal tissue such as by lavage to vaginal, rectal, urethral, buccal and sublingual tissue. Typical routes of administration include intramuscular, intraperitoneal, intradermal and subcutaneous injection. Genetic constructs may be administered by means including, but not limited to, traditional syringes, needleless injection devices, "microprojectile bombardment gene guns", or other physical

methods such as electroporation ("EP"), "hydrodynamic method", or ultrasound. DNA vaccines can be delivered by any method that can be used to deliver DNA as long as the DNA is expressed and the desired antigen is made in the cell.

[0177] In some embodiments, a DNA vaccine is delivered via known transfection reagents such as cationic liposomes, fluorocarbon emulsion, cochleate, tubules, gold particles, biodegradable microspheres, or cationic polymers. Cochleate delivery vehicles are stable phospholipid calcium precipitants consisting of phosphatidyl serine, cholesterol, and calcium; this nontoxic and noninflammatory transfection reagent can be present in a digestive system. Biodegradable microspheres comprise polymers such as poly(lactide-co-glycolide), a polyester that can be used in producing microcapsules of DNA for transfection. Lipid-based microtubes often consist of a lipid of spirally wound two layers packed with their edges joined to each other. When a tubule is used, the nucleic acid can be arranged in the central hollow part thereof for delivery and controlled release into the body of an animal.

[0178] In some embodiments, DNA vaccine is delivered to mucosal surfaces via microspheres. Bioadhesive microspheres can be prepared using different techniques and can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary tract, colon and gastrointestinal tract, offering the possibilities of localized as well as systemic controlled release of vaccines. Application of bioadhesive microspheres to specific mucosal tissues can also be used for localized vaccine action. In some embodiments, an alternative approach for mucosal vaccine delivery is the direct administration to mucosal surfaces of a plasmid DNA expression vector which encodes the gene for a specific protein antigen.

[0179] The DNA plasmid vaccines according to the present invention are formulated according to the mode of administration to be used. In some embodiments where DNA plasmid vaccines are injectable compositions, they are sterile, and/or pyrogen free and/or particulate free. In some embodiments, an isotonic formulation is preferably used. Generally, additives for isotonicity can include sodium chloride, dextrose, mannitol, sorbitol and lactose. In some embodiments, isotonic solutions such as phosphate buffered saline are preferred. In some embodiments, stabilizers include gelatin and albumin. In some embodiments, a vasoconstriction agent is added to the formulation. In some embodiments, a stabilizing agent that allows the

formulation to be stable at room or ambient temperature for extended periods of time, such as LGS or other polycations or polyanions is added to the formulation.

[0180] In some embodiments, the DNA vaccine may further comprise a pharmacologically acceptable carrier or diluent. Suitable carriers for the vaccine are well known to those skilled in the art and include but are not limited to proteins, sugars, etc. Such carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous carriers are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose and sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and antimicrobials include antioxidants, chelating agents, inert gases and the like. Preferred preservatives include formalin, thimerosal, neomycin, polymyxin B and amphotericin B.

[0181] An alternative approach to delivering the nucleic acid to an animal involves the use of a viral or bacterial vector. Examples of suitable viral vectors include adenovirus, polio virus, pox viruses such as alphaviruses, vaccinia, canary pox, and fowl pox, herpes viruses, including catfish herpes virus, adenovirus-associated vector, and retroviruses. Virus-like vectors include virosomes and virus-like particles. Exemplary bacterial vectors include attenuated forms of Salmonella, Shigella, Edwardsiella ictaluri, Yersinia ruckerii, and Listeria monocytogenes. In some embodiments, the nucleic acid is a vector, such as a plasmid, that is capable of autologous expression of the nucleotide sequence encoding the immunogenic polypeptide.

Use of Immunogenic Compositions

[0182] The immunogenic compositions, e.g., vaccines, vaccine formulations and/or pharmaceutical compositions, described herein, may be used for prophylactic and/or therapeutic treatment of herpes, including HSV-1 and particularly HSV-2. In some embodiments, such compositions are used in immunotherapy. The subject receiving the vaccination may be a male

or a female, and may be a child or adult. In some embodiments, the subject being treated is a human. In other embodiments, the subject is a non-human animal.

Prophylactic use

[0183] In prophylactic embodiments, an immunogenic composition described herein (e.g., a vaccine) is administered to a subject to induce an immune response that can help protect against the establishment of HSV-2.

[0184] In some embodiments, an immunogenic composition (e.g., vaccine composition) confers protective immunity, allowing a vaccinated individual to exhibit delayed onset of symptoms or reduced severity of symptoms (*e.g.*, reduced number of lesions at the onset of infection), as the result of his/her exposure to the vaccine (*e.g.*, a memory response). In certain embodiments, the reduction in severity of symptoms is at least 25%, 40%, 50%, 60%, 70%, 80% or even 90%. Some vaccinated individuals may display no symptoms upon contact with, HSV-2, or even no infection by HSV-2. Protective immunity is typically achieved by one or more of the following mechanisms: mucosal, humoral, or cellular immunity. Mucosal immunity is primarily the result of secretory IgA (sIGA) antibodies on mucosal surfaces of the respiratory, gastrointestinal, and genitourinary tracts. The sIGA antibodies are generated after a series of events mediated by antigen-processing cells, B and T lymphocytes, that result in sIGA production by B lymphocytes on mucosa-lined tissues of the body. Humoral immunity is typically the result of IgG antibodies and IgM antibodies in serum. For example, the IgG titer can be raised by 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold, or even 100-fold or more following administration of a vaccine formulation described herein. Cellular immunity can be achieved through cytotoxic T lymphocytes or through delayed-type hypersensitivity that involves macrophages and T lymphocytes, as well as other mechanisms involving T cells without a requirement for antibodies. In particular, cellular immunity may be mediated by T_H1 cells or T_H17 cells. Activation of T_H1 cells can be measured by secretion of IFN-γ, relative to the level of IFN-γ released in response to a polypeptide that does not generate an immunologic response. In certain embodiments, the amount of IFN-γ released is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold or even 100-fold greater. The primary result of protective immunity is the destruction of HSV-2 viral particles or inhibition of HSV-2's ability to replicate.

In some embodiments, the protective immunity conferred by presentation of antigen before exposure to HSV-2 will reduce the likelihood of seroconversion to an HSV-2-positive status.

[0185] The duration of protective immunity is preferably as long as possible. In certain embodiments, an immunogenic composition (e.g., vaccine) produces protective immunity lasting six months, one year, two years, five years, ten years, twenty years or even a lifetime.

[0186] In some embodiments, a combination of specific polypeptides may prove efficacious for inhibiting HSV-2 infection or the onset of symptoms described above. An exemplary immunogenic composition (e.g., vaccine) for prophylactic use may comprise a pharmaceutically-acceptable carrier, a first polypeptide consisting of SEQ ID NOS: 136, a second polypeptide consisting of SEQ ID NO: 1 or 4, and optionally a third polypeptide consisting of the other of SEQ ID NOS: 1 and 4, or immunogenic fragments thereof. In some embodiments, the second or third polypeptide consists of polypeptide fragments of SEQ ID NO: 1, such as the polypeptides of SEQ ID NOS: 2, 8-16, 138 and 139, or immunogenic fragments thereof. In some embodiments, an immunogenic composition (e.g., vaccine) for prophylactic use may comprise a first polypeptide consisting of SEQ ID NO: 136, a second polypeptide consisting of SEQ ID NO: 4 or SEQ ID NO: 5, a third polypeptide selected from the group consisting of SEQ ID NOS: 2, 8-16, 138 and 139, and optionally a fourth polypeptide selected from the group consisting of SEQ ID NOS: 2, 8-16, 138 and 139, or immunogenic fragments thereof.

[0187] In other embodiments, an immunogenic composition (e.g., vaccine) for prophylactic use comprises a pharmaceutically-acceptable carrier and a nucleic acid having a nucleotide sequence that encodes at least one of SEQ ID NOS: 1, 3, 5, 38, 136 or 138, or an immunogenic fragment thereof. For example, the nucleic acids can have a nucleotide sequence comprising at least one of SEQ ID NOS: 39, 46, 118, 137 or 140, or a fragment thereof that encodes an immunogenic polypeptide.

Therapeutic use

[0188] In therapeutic applications, an immunogenic composition (e.g., vaccine) comprising a polypeptide or nucleic acid described herein may be administered to a patient

suffering from HSV-2, in an amount sufficient to treat the patient. Treating the patient, in this case, may refer to delaying or reducing symptoms of HSV-2 in an infected individual. In some embodiments, treating the patient refers to reducing the duration of lesions, reducing the number of lesions, reducing the duration of symptoms per episode, and/or otherwise reducing the intensity of symptoms per episode. In certain embodiments, the vaccine reduces the duration or severity of mild symptoms; in some embodiments, the vaccine reduces the duration or severity of serious symptoms. In some embodiments, the vaccine reduces viral shedding and therefore the transmissibility of HSV-2 from the vaccinated patient. In certain embodiments, the reductions described above are at least 25%, 30%, 40%, 50%, 60%, 70%, 80% or even 90%. In certain embodiments, the reductions described above include the complete cessation of symptoms, viral shedding and/or future outbreaks (*e.g.*, by blocking the ability of the virus to establish latency in sensory ganglia).

[0189] In therapeutic embodiments, an immunogenic composition (e.g., vaccine) is administered to an individual post-infection. The immunogenic composition (e.g., vaccine) may be administered shortly after infection, *e.g.* before symptoms manifest, or may be administered during or after manifestation of symptoms. In some embodiments, the immunogenic composition (e.g., vaccine) may prevent endogenous reactivation of earlier infection. In some embodiments, a post-infection vaccine could be administered to patients in high-risk groups.

[0190] The duration of therapeutic effects of an immunogenic composition (e.g., vaccine) disclosed herein is preferably as long as possible. In certain embodiments, an immunogenic composition (e.g., vaccine) produces therapeutic effects lasting one month, two months, three months, six months, one year, two years, five years, ten years, twenty years or even a lifetime.

[0191] In some embodiments, a combination of specific polypeptides may prove efficacious for treating a patient suffering from HSV-2 as described above. An exemplary immunogenic composition (e.g., vaccine) for therapeutic use may comprise a pharmaceutically-acceptable carrier, a first polypeptide consisting of SEQ ID NOS: 136, a second polypeptide consisting of SEQ ID NO: 1 or 4, and optionally a third polypeptide consisting of the other of SEQ ID NOS: 1 and 4, or immunogenic fragments thereof. In some embodiments, the second or third polypeptide consists of polypeptide fragments of SEQ ID NO: 1, such as the polypeptides

of SEQ ID NOS: 2, 8-16, 138 and 139, or immunogenic fragments thereof. In some embodiments, immunogenic composition (e.g., vaccine) for therapeutic use may comprise a first polypeptide consisting of SEQ ID NO: 136, a second polypeptide consisting of SEQ ID NO: 4 or SEQ ID NO: 5, a third polypeptide selected from the group consisting of SEQ ID NOS: 2, 8-16, 138 and 139, and optionally a fourth polypeptide selected from the group consisting of SEQ ID NOS: 2, 8-16, 138 and 139, or immunogenic fragments thereof.

[0192] In other embodiments, an immunogenic composition (e.g., vaccine) for therapeutic use comprises a pharmaceutically-acceptable carrier and a nucleic acid having a nucleotide sequence that encodes at least one of SEQ ID NOS: 1, 3, 5, 38, 136 or 138 or an immunogenic fragment thereof. For example, the nucleic acids can have a nucleotide sequence comprising at least one of SEQ ID NOS: 39, 46, 118, 137 or 140, or a fragment thereof that encodes an immunogenic polypeptide.

Assaying vaccination efficacy

[0193] The efficacy of vaccination with an immunogenic composition (e.g., vaccine) disclosed herein may be determined in a number of ways.

[0194] Efficacy may be assayed in various model systems. Suitable model systems used to study HSV-2 include a guinea pig model and a mouse model, as described in the examples below. Briefly, the animals are vaccinated with immunogenic composition (e.g., vaccine) and then challenged with HSV-2 or the immunogenic composition (e.g., vaccine) is administered to already-infected animals. The response of the animals to the HSV-2 challenge or the immunogenic composition (e.g., vaccine) is then compared with control animals, using one of the measures described above. A similar assay could be used for clinical testing of humans. The treatment and prophylactic effects described above represent additional ways of determining efficacy of an immunogenic composition (e.g., vaccine).

[0195] In addition, efficacy may be evaluated by *in vitro* immunization of naïve human peripheral blood mononuclear cells (PBMC), where APCs are exposed to the immunogenic composition (e.g., vaccine) and then the APCs are co-cultured with naïve T cells from the same

donor to evaluate the primary response to immunization in a test tube. An activation of the T-cells by 1.5-fold, 2-fold, 5-fold, 10-fold, 20-fold, 50-fold or 100-fold or more relative to activation of T-cells using APCs not exposed to an immunogenic composition (e.g., vaccine), in certain embodiments, is considered an adequate response.

[0196] Efficacy may further be determined by viral neutralization assays. Briefly, animals are immunized and serum is collected on various days post-immunization. Serial dilutions of serum are pre-incubated with virus during which time antibodies in the serum that are specific for the virus will bind to it. The virus/serum mixture is then added to permissive cells to determine infectivity by a plaque assay. If antibodies in the serum neutralize the virus, there are fewer plaques compared to the control group.

Antiviral Therapy

[0197] Methods described herein include combination of an immunogenic composition described herein and antiviral therapy. Any antiviral therapy can be combined with an immunogenic composition described herein. Antiviral therapy is a class of medications used specifically for treating viral infections. Most antivirals are used to treat specific viral infections; however, broad spectrum antivirals are effective against a wide range of viruses. Antivirals typically do not destroy a target pathogen, but instead inhibits its replication or development. Most antiviral therapeutics available are used to treat HIV, herpes viruses, hepatitis B and C viruses, and influenza A and B viruses.

Valacyclovir

[0198] Valacyclovir (or valaciclovir) is an antiviral drug approved for use in adult patients with, among other things, cold sores (e.g., herpes labialis), genital herpes (including initial episode, recurrent episodes, suppressive therapy and reduction of transmission) and herpes zoster. Valacyclovir is a prodrug converted in vivo to acyclovir. It is sold under the name Valtrex® (valacyclovir hydrochloride).

[0199] To treat cold sores in an adult, the current approved dosage of valacyclovir is 2 g twice daily for 1 day taken 12 hours apart. Therapy is initiated at the earliest symptom of a cold sore (e.g., tingling, itching or burning). To treat an initial episode of genital herpes in an adult the

current approved dosage of valacyclovir is 1 g twice daily for 10 days. The therapy is most effective when administered within 48 hours of the onset of signs and symptoms. To treat a recurrent episode of genital herpes in an adult, the current approved dosage of valacyclovir is 50 mg twice daily for 3 days. Treatment is initiated at the first sign or symptom of an episode. To provide suppressive therapy for recurrent genital herpes in an adult, the current approved dosage of valacyclovir is 1 g once daily in patients with normal immune function. In patients with a history of 9 or fewer recurrences per year, an alternative dose is 500 mg once daily. In HIV-1-infected patients with a CD4+ cell count greater than or equal to 100 cells/mm^3, the current approved dosage of valacyclovir for chronic suppressive therapy of recurrent genital herpes is 500 mg twice daily. To reduce transmission of genital herpes in adults with a history of 9 or fewer recurrences per year, the current approved dosage of valacyclovir is 500 mg once daily for the source partner. The current approved dosage of valacyclovir for treatment of herpes zoster is 1 gram 3 times daily for 7 days. Therapy should be initiated at the earliest sign or symptom of herpes zoster and is most effective when started within 48 hours of the onset of rash.

[0200] Valacyclovir is also approved for use in pediatric patients for the treatment of cold sores (e.g., herpes labialis) and chicken pox. The current approved dosage of valacyclovir for the treatment of cold sores in pediatric patients aged greater than or equal to 12 years is 2 grams twice daily for 1 day taken 12 hours apart. Therapy should be initiated at the earliest symptom of a cold sore (e.g., tingling, itching, or burning). The current approved dosage of valacyclovir for treatment of chickenpox in immunocompetent pediatric patients aged 2 to less than 18 years is 20 mg/kg administered 3 times daily for 5 days. The total dose should not exceed 1 gram 3 times daily. Therapy should be initiated at the earliest sign or symptom.

Famciclovir

[0201] Famciclovir is an antiviral drug approved for use in immunocompetent adult patients with, among other things, cold sores (e.g., herpes labialis), genital herpes (including recurrent episodes and suppressive therapy), and herpes zoster. Famciclovir is also approved for use in HIV infected adult patients with recurrent orolabial or genital herpes. Famciclovir is sold under the name FAMVIR®.

[0202] To treat recurrent cold sores in an immunocompetent adult, the current approved dosage of famciclovir is 1500 mg as a single dose. Therapy is initiated at the earlies symptom of a cold sore (e.g., tingling, itching, burning, pain or lesion). To treat a recurrent episode of genital herpes in an immunocompetent adult the current approved dosage of famciclovir is 100 mg twice daily for 1 day. Therapy should be initiated at the first sign or symptom of a recurrent episode (e.g., tingling, itching, burning pain or lesion). To provide suppressive therapy for recurrent genital herpes in an immunocompetent adult, the current approved dosage of 250 mg twice daily. To treat herpes zoster in an immunocompetent adult, the current approved dosage of famciclovir is 500 mg every 8 hours for 7 days. Therapy should be initiated as soon as herpes zoster is diagnosed.

[0203] To treat recurrent orolabial or genital herpes in HIV-infected adult patients, the current approved dosage of famciclovir is 500 mg twice daily for 7 days. Therapy should be initiated at the first sign or symptom of a recurrent episode (e.g., tingling, itching, burning, pain or lesion).

Acyclovir

[0204] Acyclovir is guanosine analog approved for use in immunocompromised adult patients with, among other things, initial and recurrent mucosal and cutaneous herpes simplex (due to HSV-1 and HSV-2), severe initial clinical episodes of herpes genitalis, and varicella-zoster (shingles). It is also approved for use in adult patients with, among other things, herpes simplex encephalitis and in neonatal herpes simplex virus infection. Acyclovir is sold under the name ZOVIRAX.

[0205] To treat mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) infection in immunocompromised patients, the current approved dosage of acyclovir for adults and adolescents (12 years of age and older) is 5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days. In children less than 12 years of age the current approved dosage of acyclovir is 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days. To treat severe initial clinical episodes of herpes genitalis infection in adults and adolescents (12 years of age and

older) the current approved dosage of acyclovir is 5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 5 days.

[0206] To treat herpes simplex encephalitis in adults and adolescents (12 years of age and older) the recommended dosage of acyclovir is 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. The current approved pediatric (3 months to 12 years of age) dosage of acyclovir for the treatment of herpes simplex encephalitis is 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. To treat neonatal herpes simplex virus infection (birth to 3 months) the current approved dosage of acyclovir is 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

[0207] To treat varicella zoster infection in immunocompromised adult or adolescent (12 years of age and older) patients, the current approved dosage is of acyclovir 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days. For the treatment of pediatric (under 12 years of age) patients, the current approved dosage of acyclovir is 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Other antiviral therapies for HSV

[0208] In addition to acyclovir and its prodrug valacyclovir, the nucleoside analogs penciclovir and trifluridine are approved for treatment of HSV. Penciclovir is not orally bioavailable and as such is only used as a topical formulation for labial herpes. The nucleoside analog trifluridine, a modified form of deoxyuridine, is used to treat herpes keratitis and is also active against other viruses such as vaccinia virus and some adenovirus strains. Docosanol is a saturated fatty alcohol used for topical treatment of recurrent labial herpes; its proposed mode of action is the prevention of viral envelope fusion with the host cell membrane. Treatment with acyclovir, in combination with hydrocortisone, results in an increase in the number of prodrome only episodes of recurrent labial herpes such that outbreak is prevented.

Small molecule compounds are being developed for the treatment of genital or labial HSV infections. Two compounds of interest, amenamevir and pritelivir belong to a class of helicase-primase inhibitors. The viral helicase-primase enzyme complex is a heterotrimer consisting of viral UL5 helicase, UL52 primase, and UL8, an accessory protein without

enzymatic function. It is required for DNA unwinding at the replication fork and synthesis of primers during virus replication. Since there is no eukaryotic homologue of the helicase-primase complex and since it is essential for viral replication, the helicase-primase complex represents an attractive target for new drug development. Furthermore, helicase-primase inhibitors do not need to become activated by viral enzymes and therefore, can protect both infected and uninfected cells from infection. Amenamevir is a helicase-primase inhibitor with activity against both HSV and VZV. In early studies, the efficacy of once-daily amenamevir was comparable to that of valacyclovir administered twice daily for 3 days with time to lesion healing shortened by 1-2 days. Pritelivir has shown efficacy in reduction of viral shedding and lesion rate in patients with genital herpes. Additional antivirals are described in, e.g., Birkmann et al., Curr Opin. Virol. 18:9-13 (2016)).

Uses of Immunogenic Compositions

Defense against HSV infection

[0209] Immunogenic compositions of the present disclosure are designed to elicit an immune response against HSV-2. Compositions described herein may stimulate an innate immune response, an antibody response or a cell-mediated immune response, or a combination of these responses, in the subject to which it is administered. In some embodiments, the composition stimulates immune cells at the peripheral site of infection or sensory ganglia, such as neutrophils, macrophages, and NK cells. The composition may stimulate infiltration by macrophages; production of antiviral compounds such as nitric oxide, TNF-α, interferons (IFN), and interleukin 12 (IL-12) by neutrophils; and/or stimulation of NK cells to produce IFN-γ. IL-2, IFN-α and IFN-β production may also be triggered by the polypeptides of the present composition, and are believed to aid in controlling infection.

[0210] In some embodiments, the composition comprises antigens that stimulate production of neutralizing antibodies. Neutralizing antibodies may target the glycoproteins of the viral envelope, which mediate the interaction of virions with host cell and are responsible for attachment, binding, and entry of HSV-2 into cells. Accordingly, an exemplary composition comprises one or more glycoproteins described above or encoded by nucleic acids described

above. Immunogenic antigens and/or epitopes as described herein may be administered separately, in series, or in combination with one another.

[0211] In some embodiments, the composition elicits a cell-mediated response, which may involve $CD4^+$ T cells, $CD8^+$ T cells and/or production of antiviral cytokines. The composition may trigger IL-17 secretion by T_H17 cells. The composition may trigger IFN-γ secretion, for example through the activation of the innate immune response, and mediate $CD8^+$ T cell clearing of the virus. IFN-γ is also secreted by T_H1 cells, T_C cells, dendritic cells, and NK cells, and the composition may trigger IFN-γ secretion by any of these cell types. Such activity of $CD8^+$ T cells may be cytolytic, or, alternately, may be regulated by inhibitor molecules on the surface of the neurons which prevent neuronal killing. $CD4^+$ and/or $CD8^+$ T cells may play a role in maintaining latency of the virus, thus preventing reactivation. In some embodiments, the composition boosts a $CD4^+$ T cell response and/or a $CD8^+$ T cell response that prevents reactivation of the virus from its latent state.

[0212] In some embodiments, the composition blocks the ability of HSV to evade the host immune response, or, alternately, boosts immune responses normally evaded by HSV. In some embodiments, the composition inhibits HSV-2 from shifting the immunological balance towards tolerance of HSV antigens. HSV-2 may mediate tolerance through T_H2 cells. First, HSV-2 may induce suppressor T cells, such as $CD4^+$ $CD25^+$ T cells and Tr1 cells that secrete IL-10, a T_H2 cytokine. T_H2 cytokines downregulate costimulatory molecules and inhibit the maturation and function of antigen-presenting dendritic cells. In addition, infection with HSV-2 inhibits the maturation and migration of dendritic cells, which are essential for efficient induction of $CD8^+$ killer T cells. Notably, T_H2 cytokines are produced during recurrence of HSV-2 infection, in contrast to T_H1 cytokines, which are produced during recurrence-free episodes. Thus, in certain embodiments, the compositions of the invention repress suppressor T cells and/or induce maturation or migration or both of dendritic cells.

[0213] In some embodiments, methods of inducing an immune response against HSV-2 in a mammal comprise administering the compositions described above. The composition may be used to induce an immune response at different time points, such as before exposure to HSV-2, after initial infection with HSV-2, before or after HSV-2 has established latency, before or

after HSV-2 shedding occurs, and/or before or after recurrent outbreaks occur. In some embodiments, an immune response against HSV-2 may be induced at one or more of the timepoints above. The composition may induce a T_H1 response and/or a T_H17 response but not a T_H2 response, or may activate the responses at the same time or at different times.

[0214] In some embodiments, administration of the composition reduces symptoms associated with initial infection, latency, or recurrent infection with HSV. Such a composition may reduce incidence and/or severity of lesions, sores, pain, irritation, itching, fever, malaise, headache, viral shedding, or prodromes associated with HSV infection or outbreak.

[0215] In some embodiments, one or more antibodies to antigens of HSV-2 may be administered to individuals in order to produce passive immunity. Passive immunity results from the transfer of active humoral immunity in the form of ready-made antibodies, from one individual to another. Passive immunization may be used when there is a high risk of infection and insufficient time for the body to develop its own immune response, or to reduce the symptoms of ongoing or immunosuppressive diseases. Adoptive transfer of T cells may provide another method of eliciting an immune response to HSV-2 antigens in patients. In one embodiment, autologous T cells may be expanded on APCs presenting the antigens derived from the polypeptides described above. Subsequently, the expanded HSV-2-specific T cells are transferred back into the patient from which the T cells were derived.

Diagnostic uses

[0216] This application provides, *inter alia,* a rapid, inexpensive, sensitive, and specific method for detection of HSV-2 in patients. In this respect it should be useful to hospitals and physicians examining and treating patients with or at risk for HSV-2 infection. As used herein, "patient" refers to an individual (such as a human) that either has an HSV-2 infection or has the potential to contract an HSV-2 infection.

[0217] In some embodiments, one may use an antibody against one of the polypeptides described herein, such as those of Table 1 and/or Table 2, to detect HSV-2 in an individual. The instant disclosure also provides a method of phenotyping biological samples from patients suspected of having a HSV-2 infection that involves: (a) rendering a biological sample amenable

to immunoassay, if necessary; (b) contacting the sample with an appropriate HSV-2-specific antibody or antigen-binding portion thereof under conditions that allow for binding of the antibody or antigen-binding portion to an epitope of HSV-2; and (c) determining if the sample shows the presence of HSV-2 as compared to a control tissue; where if the test tissue shows the presence of HSV-2, the patient is identified as likely having a HSV-2 infection.

[0218] Alternatively, one may use the polypeptides described above to detect anti-HSV-2 antibodies in an individual. The instant disclosure also provides a method of phenotyping biological samples from patients suspected of having a HSV-2 infection: (a) rendering a biological sample amenable to an affinity assay such as ELISA, if necessary; (b) contacting the sample with a HSV-2-specific antigen or portion thereof under conditions that allow for binding of the antigen to any host antibodies present in the sample; and (c) determining if the sample shows the presence of HSV-2 as compared to a control tissue; where if the test tissue shows the presence of HSV-2, the patient is identified as likely having a HSV-2 infection. The aforementioned test may be appropriately adjusted to detect other viral infections, for instance by using a homolog (from another viral species) of the proteins described above, such as in Table 1 and/or Table 2.

[0219] A number of methods for measuring antibody-antigen binding are known in the art, including ELISA (enzyme-linked immunosorbent assay), Western blotting, competition assay, and spot-blot. The detection step may be, for instance, chemiluminescent, fluorescent, or colorimetric. One suitable method for measuring antibody-protein binding is the Luminex xMAP system, where peptides are conjugated to a dye-containing microsphere. Certain systems, including the xMAP system, are amenable to measuring several different markers in multiplex, and could be used to measure levels of antibodies at once. In some embodiments, other systems are used to assay a plurality of markers in multiplex. For example, profiling may be performed using any of the following systems: antigen microarrays, bead microarrays, nanobarcodes particle technology, arrayed proteins from cDNA expression libraries, protein in situ array, protein arrays of living transformants, universal protein array, lab-on-a-chip microfluidics, and peptides on pins. Another type of clinical assay is a chemiluminescent assay to detect antibody binding. In some such assays, including the VITROS Eci anti-HCV assay, antibodies are bound

to a solid-phase support made up of microparticles in liquid suspension, and a surface fluorometer is used to quantify the enzymatic generation of a fluorescent product.

[0220] In other embodiments, one may use the polypeptides described above, such as those of Table 1 and/or Table 2, to detect T cells that are specific to HSV-2. The instant disclosure provides a method of phentoyping biological samples from patients suspected of having a HSV-2 infection, involving (a) rendering a biological sample amenable to an assay for activation of T cells, if necessary, (b) contacting the sample with a HSV-2-specific polypeptide or portion thereof under conditions that allow APCs to process the polypeptide, and (c) determining activation of the T cells in response to the HSV-2-specific polypeptide, where an elevated T cell activation relative to an uninfected patient indicates HSV-2 infection. This diagnostic assay is intended to detect the presence of HSV-2-specific T cells in any patients, including those patients who have been exposed to HSV-2 but have not seroconverted to produce detectable levels of anti-HSV-2 antibodies.

[0221] T cell activation may be measured using many assays, including cytokine-specific ELISA, cell proliferation measured by tritiated thymidine incorporation or membrane intercolating (PKH-67) or cytoplasmic (CFSE) dyes, ELISPOT, flow cytometry, and bead arrays. In addition, one may measure the T cell response in T cell lines or in T cell hybridomas from mice or humans that are specific for the antigens. Readouts for activated T cells include proliferation, cytokine production, or readout of a surrogate enzyme expressed by the hybridoma that is induced when the T cell or T cell hybridoma is activated in response to an antigen. For example, activation of a T cell response may be detected by T cell hybridoma that is engineered to produce β-galactosidase. β-galactosidase may be detected through the use of colorimetric □□galactosidase substrates such as chlorophenyl red □-D galactopyranoside (CPRG).

[0222] Infection with HSV-2 may be acute or latent. In some embodiments, if the biological sample shows the presence of HSV-2, one may administer a therapeutically effective amount of the compositions and therapies described herein to the patient. The biological sample may comprise, for example, blood, semen, urine, vaginal fluid, mucus, saliva, feces, urine, cerebrospinal fluid, or a tissue sample. In some embodiments, the biological sample is an organ

intended for transplantation. In certain embodiments, before the detection step, the biological sample is subject to culture conditions that promote the growth of HSV-2.

[0223] The diagnostic tests herein may be used to detect HSV-2 in a variety of samples, including samples taken from patients and samples obtained from other sources. For example, the diagnostic tests may be used to detect HSV-2 on objects such as medical instruments. In some embodiments, the tests herein may be performed on samples taken from animals such as agricultural animals (cows, pigs, chickens, goats, horses and the like), companion animals (dogs, cats, birds, and the like), or wild animals. In certain embodiments, the tests herein may be performed on samples taken from cell cultures such as cultures of human cells that produce a therapeutic protein, cultures of bacteria intended to produce a useful biological molecule, or cultures of cells grown for research purposes.

[0224] The invention also includes a method of determining the location of a HSV-2 infection in a patient comprising: (a) administering a pharmaceutical composition comprising a labeled HSV-2 antibody or antigen-binding portion thereof to the patient, (b) detecting the label, and (c) determining if the patient has HSV-2 compared to a control. In certain embodiments, the method further comprises, if the patient has an HSV-2 infection, administering a therapeutically effective amount of a composition described herein to the patient. The method may further comprise determining the infected cell types and/or volume of the HSV-2 in the patient. This method may be used to evaluate the spread of HSV-2 in the patient and determine whether a localized therapy is appropriate.

[0225] In some embodiments, the polypeptides described herein may be used to make a prognosis of the course of infection. In some embodiments, T cell or antibody responses specific for the polypeptides herein may be detected in a sample taken from a patient. If antibodies or T cells are present at normal levels, it would indicate that the patient has raised an effective immune response against the pathogen. If antibodies or T cells are absent, or present at reduced levels, it would indicate that the patient is failing to raise a sufficient response against the pathogen, and a more aggressive treatment would be recommended. In some embodiments, antibody or T cells present at reduced levels refers to responses that are present at less than 50%, 20%, 10%, 5%, 2%, or 1% the typical level in a patient with a protective immune response. T

cell responses may be detected by methods known in the art such as T cell proliferation, ELISPOT or ELISA, and antibodies may be detected by affinity for any of the antigens described herein, using methods known in the art such as ELISA.

[0226] In some embodiments, detection of T cells specific for HSV-2 antigens may be used to predict the progress and symptoms of HSV-2 infection in a patient. After infection with HSV-2, some patients remain asymptomatic, although the virus may establish latency. Other patients exhibit symptoms of HSV-2 infection, and may experience recurrent outbreaks. The HSV-2 antigens found in asymptomatic patients may differ from those antigens found in patients who present symptoms and/or recurrent outbreaks. Accordingly, the detection methods of the present invention may be used to distinguish between subgroups within the population of patients infected with HSV-2. Subgroups may be further divided into patients who experience frequent outbreaks and those who infrequently or never experience outbreaks, or patients who shed high levels of virus and those who shed low levels or do not shed. The categorization of patients, based on the presence and levels of T cell responses to certain HSV-2 antigens but not others, may help health care practitioners to determine appropriate treatment regimens. Similarly, differences in the magnitude of T cell responses and/or differences in the combination and levels of cytokines produced by T cells may also be used to predict the progress and symptoms of HSV-2 infection in a patient. Thus, an infected patient whose complement of HSV-2 antigens to which T cells respond predicts severe symptoms, frequent outbreaks, and/or high levels of viral shedding may require more intensive antiviral therapy and/or a longer course of therapeutic treatment than a patient whose complement of HSV-2 antigens predicts an asymptomatic infection.

[0227] It will be understood by one of skill in the art that the methods herein are not limited to detection of HSV-2. Other embodiments include the detection of related viruses including viruses with proteins homologous to the proteins described above, such as those in Table 1 and/or Table 2. Such related viruses include, for example, other members of the *Herpesviridae* family. Depending on the homology, these related viruses may also include viruses that are not members of the *Herpesviridae* family.

Use in groups with increased risk for infection by HSV-2

[0228] Essentially any individual has a certain risk of infection with HSV-2. However, certain sub-populations have an increased risk of infection. In some embodiments, patients receiving an immunogenic composition and/or antiviral therapy are immunocompromised.

[0229] An immunocompromising condition arising from a medical treatment is likely to expose the individual in question to a higher risk of infection. It is possible to treat an infection prophylactically in an individual having the immunocompromised condition before or during treatments known to generate such a condition. By prophylactically treating with the antigen before or during a treatment known to generate such a condition it is possible to prevent a subsequent infection or to reduce the risk of the individual contracting an infection due to the immunocompromised condition. Should the individual contract an infection, *e.g.*, following a treatment leading to an immunocompromised condition, it is also possible to treat the infection by administering to the individual an antigen composition.

[0230] In certain embodiments, the compositions are administered to children or adult patients. In other embodiments, compositions are appropriate for pregnant women who were infected before becoming pregnant, or who became infected during pregnancy, such as to inhibit infection of a fetus or baby. The compositions may also be administered to neonates and infants who became infected in utero or during delivery.

Doses and Routes of Administration

Dosage amounts and timing

[0231] The amount of antigen in each vaccine dose is selected as an effective amount, which induces a prophylactic or therapeutic response, as described above, in either a single dose or over multiple doses. Preferably, the dose is without significant adverse side effects in typical vaccinees. Such amount will vary depending upon which specific antigen is employed. Generally, it is expected that a dose will comprise 1-1000 μg of protein, in some instances 2-100 μg, for instance 4-40 μg. Alternatively, a dose will comprise 10-6000 μg of nucleic acid, in some instances 20-4000 μg, for instance 30-4000 μg. An optimal amount for a particular vaccine can

be ascertained by standard studies involving observation of antibody titers, T cell activation levels, and other responses in subjects. In some embodiments, the appropriate amount of antigen to be delivered will depend on the age, weight, and health (*e.g.*, immunocompromised status) of a subject. When present, typically an adjuvant will be present in amounts from 1 μg – 250 μg per dose, for example 50-150 μg, 75-125 μg or 100 μg.

[0232] In some embodiments, only one dose of the vaccine is administered to achieve the results described above. In other embodiments, following an initial vaccination, subjects receive one or more boost vaccinations, for a total of two, three, four or five vaccinations. Advantageously, the number is three or fewer. A boost vaccination may be administered, for example, about 1 month, 2 months, 4 months, 6 months, or 12 months after the initial vaccination, such that one vaccination regimen involves administration at 0, 0.5-2 and 4-8 months. It may be advantageous to administer split doses of vaccines which may be administered by the same or different routes.

[0233] In some embodiments, the invention supplies a treatment regimen comprising a first dose of vaccine and a second, third or fourth dose of vaccine (a boost vaccine). In exemplary embodiments, a first dose of vaccine comprises one or more polypeptide antigens, or nucleic acids encoding one or more polypeptide antigens, or a combination of one or more polypeptide antigens and nucleic acids encoding the same or other protein antigens. In some embodiments, a boost vaccine is formulated with the same polypeptide antigens, nucleic acids, or polypeptide antigens and nucleic acids as the first dose. In some embodiments, a boost vaccine is formulated with different polypeptide antigens, nucleic acids, or polypeptide antigens and nucleic acids from the first dose. In some embodiments, the first dose may comprise only polypeptide antigens and boost vaccine may comprise only nucleic acids, or the first dose may comprise only nucleic acids and boost vaccine may comprise only polypeptide. In some embodiments, the first dose may comprise polypeptide antigens and nucleic acids, and boost vaccine may comprise only protein antigens or only nucleic acids. In some embodiments, the first dose may comprise only protein antigens or only nucleic acids, and boost vaccine may comprise protein antigens and nucleic acids. In certain embodiments where the boost vaccine is a polypeptide, the polypeptide is gL2 (SEQ ID NO: 3) or ICP4 (SEQ ID NO: 1) or an

immunogenic fragment thereof (e.g., ICP4.2, and gL2s v.2, SEQ ID NOS: 2 and 136), optionally in combination with one or more of the adjuvants described above, particularly one or more of the ISCOMs. Such polypeptide boost vaccines are particularly useful in conjunction with any one of the nucleic acid vaccines described above (e.g., nucleic acids having nucleotide sequences that encode at least one of SEQ ID NOS: 1, 3, 5, 38, 136 or 138, or an immunogenic fragment thereof).

[0234] The pharmaceutical compositions described herein may take on a variety of dosage forms. In certain embodiments, the composition is provided in solid or powdered (*e.g.*, lyophilized) form; it also may be provided in solution form. In certain embodiments, a dosage form is provided as a dose of lyophilized composition and at least one separate sterile container of diluent.

[0235] In some embodiments, the antigen is delivered to a patient at an amount of 1μmol per dose. In some embodiments, the antigen is delivered at a dose ranging from 10 nmol to 100 nmol per dose. The appropriate amount of antigen to be delivered may be determined by one of skill in the art. In some embodiments, the appropriate amount of antigen to be delivered will depend on the age, weight, and health (*e.g.*, immunocompromised status) of a subject.

[0236] Pharmaceutical compositions disclosed herein are (in some embodiments) administered in amounts sufficient to elicit production of antibodies as part of an immunogenic response. In some embodiments, the composition may be formulated to contain 5 μg /0.5 ml or an amount ranging from 10 μg /1 ml to 200 μg /1 ml of an antigen. In other embodiments, the composition may comprise a combination of antigens. The plurality of antigens may each be the same concentration, or may be different concentrations.

[0237] In some embodiments, the composition will be administered in a dose escalation manner, such that successive administrations of the composition contain a higher concentration of composition than previous administrations. In some embodiments, the composition will be administered in a manner such that successive administrations of the composition contain a lower concentration of composition than previous administrations.

[0238] In therapeutic applications, compositions are administered to a patient suffering from a disease in an amount sufficient to cure or at least partially arrest the disease and its complications.

[0239] Therapeutic applications of a composition described herein include reducing transmissibility, slowing disease progression, reducing viral shedding, or eliminating recurrent infections in patients that have been infected with HSV-2, such as by 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20% or 10% of the levels at which they would occur in individuals who are not treated with the composition. The composition may also reduce the quantity of HSV-2 shed by infected individuals, inhibit the expression of proteins required for reactivation of HSV-2 from the latent stage in infected patients, and/or inhibit replication of HSV-2 in neurons of infected patients, such as by 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the levels at which they would occur in individuals not treated with the composition.

[0240] In prophylactic embodiments, compositions are administered to a human or other mammal to induce an immune response that can inhibit the establishment of an infectious disease or other condition. In some embodiments, a composition may partially block the virus from establishing latency or reduce the efficiency with which latency is established.

[0241] In some embodiments, only one dose (administration) of the composition is given. In other embodiments, the composition is administered in multiple doses. In various embodiments, the composition is administered once, twice, three times, or more than three times. The number of doses administered to a subject is dependent upon the antigen, the extent of the disease or the expected exposure to the disease, and the response of a subject to the composition.

[0242] In some embodiments, the compositions are administered in combination with antimicrobial molecules. Antimicrobial molecules may include antiviral molecules. Many antiviral molecules are currently known in the art, and target one or more stage of the viral life cycle, including viral attachment to host cells, release of viral genes and/or enzymes into the host cell, replication of viral components using host-cell machinery, assembly of viral components into complete viral particles, and release of viral particles to infect new hosts.

Routes of administration

[0243] The vaccine formulations and pharmaceutical compositions herein can be delivered by administration to an individual, typically by systemic administration (*e.g.*, intravenous, intraperitoneal, intramuscular, intradermal, subcutaneous, transdermal, subdermal, intracranial, intranasal, mucosal, anal, vaginal, oral, sublingual, buccal route or they can be inhaled) or they can be administered by topical application.

[0244] In some embodiments, the composition may be administered directly to the likely sites of infection. In female patients, the composition may be applied topically to mucosal membranes, or delivered vaginally or rectally using devices and methods known in the art. The vaginal and rectal routes of delivery permit extended, continuous or pulsed delivery and administration of composition dosages, and may be administered either before or after exposure to HSV, depending on the use of a prophylactic or therapeutic composition. In male patients, the composition may be applied topically to the skin or mucosal membranes, or delivered rectally. In both patient populations, the composition may also be targeted to the sensory ganglia.

[0245] An HSV-2 vaccine or pharmaceutical composition is often administered via the intramuscular route. Typically, in this route, the vaccine is injected into an accessible area of muscle tissue. Intramuscular injections are, in some embodiments, given in the deltoid, vastus lateralis, ventrogluteal or dorsogluteal muscles. The injection is typically given at an approximately 90° angle to the surface of the skin, so the vaccine penetrates the muscle.

[0246] An HSV-2 vaccine may also be administered subcutaneously. The injection is typically given at a 45° angle to the surface of the skin, so the vaccine is administered to the subcutis and not the muscle.

[0247] In some embodiments, the HSV-2 vaccine is administered intradermally. Intradermal administration is similar to subcutaneous administration, but the injection is not as deep and the target skin layer is the dermis. The injection is typically given at a 10-15° angle to the surface of the skin, so the vaccine is delivered just beneath the epidermis.

[0248] In some embodiments, the HSV-2 vaccine is administered by electroporation. Delivery by electroporation may be intramuscular or intradermal. Suitable devices for

electroporation include devices made by Inovio Pharmaceuticals, Inc. (Blue Bell, PA) and the TriGrid™ Delivery System made by Ichor Medical Systems, Inc. (San Diego, CA).

Formulations

[0249] The vaccine formulation may be suitable for administration to a human patient, and vaccine preparation may conform to USFDA guidelines. In some embodiments, the vaccine formulation is suitable for administration to a non-human animal. In some embodiments, the vaccine is substantially free of either endotoxins or exotoxins. Endotoxins include pyrogens, such as lipopolysaccharide (LPS) molecules. The vaccine may also be substantially free of inactive protein fragments. In some embodiments, the vaccine has lower levels of pyrogens than industrial water, tap water, or distilled water. Other vaccine components may be purified using methods known in the art, such as ion-exchange chromatography, ultrafiltration, or distillation. In other embodiments, the pyrogens may be inactivated or destroyed prior to administration to a patient. Raw materials for vaccines, such as water, buffers, salts and other chemicals may also be screened and depyrogenated. All materials in the vaccine may be sterile, and each lot of the vaccine may be tested for sterility. Thus, in certain embodiments the endotoxin levels in the vaccine fall below the levels set by the USFDA, for example 0.2 endotoxin (EU)/kg of product for an intrathecal injectable composition; 5 EU/kg of product for a non-intrathecal injectable composition, and 0.25-0.5 EU/ml for sterile water.

[0250] In some embodiments, the vaccine comprising a polypeptide contains less than 5%, 2%, 1%, 0.5%, 0.2%, 0.1% of other, undesired unpolypeptides, relative to the amount of desired polypeptides. In some embodiments, the vaccine contains less than 5%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, or less than 0.1% DNA and/or RNA.

[0251] It is preferred that the vaccine has low or no toxicity, within a reasonable risk-benefit ratio.

[0252] The formulations suitable for introduction of the pharmaceutical composition vary according to route of administration. Formulations suitable for parenteral administration, such as, for example, by intraarticular (in the joints), intravenous, intramuscular, intradermal, intraperitoneal, intranasal, and subcutaneous routes, include aqueous and non-aqueous, isotonic

sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials.

[0253] Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described. Cells transduced by the packaged nucleic acid can also be administered intravenously or parenterally.

[0254] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the polypeptides or packaged nucleic acids suspended in diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, tragacanth, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art. The pharmaceutical compositions can be encapsulated, *e.g.*, in liposomes, or in a formulation that provides for slow release of the active ingredient.

[0255] The antigens, alone or in combination with other suitable components, can be made into aerosol formulations (*e.g.*, they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

[0256] Suitable formulations for vaginal or rectal administration include, for example, suppositories, which consist of the polypeptides or packaged nucleic acids with a suppository base. Suitable suppository bases include natural or synthetic triglycerides or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the polypeptides or packaged nucleic acids with a base, including, for example, liquid triglycerides, polyethylene glycols, and paraffin hydrocarbons. The formulation may be suitable for administration to a human patient, and the preparation may conform to US FDA guidelines. In some embodiments, the formulation is suitable for administration to a non-human animal. In some embodiments, the composition is substantially free of either endotoxins or exotoxins. Endotoxins may include pyrogens, such as lipopolysaccharide (LPS) molecules. The composition may also be substantially free of inactive protein fragments which may cause a fever or other side effects. In some embodiments, the composition contains less than 1%, less than 0.1%, less than 0.01%, less than 0.001%, or less than 0.0001% of endotoxins, exotoxins, and/or inactive protein fragments. In some embodiments, the composition has lower levels of pyrogens than industrial water, tap water, or distilled water. Other components may be purified using methods known in the art, such as ion-exchange chromatography, ultrafiltration, or distillation. In other embodiments, the pyrogens may be inactivated or destroyed prior to administration to a patient. Raw materials for compositions, such as water, buffers, salts and other chemicals may also be screened and depyrogenated. All materials in the composition may be sterile, and each lot of the composition may be tested for sterility. Thus, in certain embodiments the endotoxin levels in the composition fall below the levels set by the USFDA: 0.2 endotoxin (EU)/kg of product for an intrathecal injectable composition; 5 EU/kg of product for a non-intrathecal injectable composition, and 0.25-0.5 EU/ml for sterile water.

[0257] In certain embodiments, the preparation comprises less than 50%, 20%, 10%, or 5% (by dry weight) contaminating protein. In certain embodiments, the desired molecule is present in the substantial absence of other biological macromolecules, such as other proteins (particularly other proteins which may substantially mask, diminish, confuse or alter the characteristics of the component proteins, either as purified preparations or in their function in the subject reconstituted mixture). In certain embodiments, at least 80%, 90%, 95%, 99%, or

99.8% (by dry weight) of biological macromolecules of the same type present (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 5000, can be present).

[0258] It is preferred that the composition has low or no toxicity, within a reasonable risk-benefit ratio. In certain embodiments, the composition comprises ingredients at concentrations that are less than LD_{50} measurements for the animal being treated with the composition. LD_{50} measurements may be obtained in mice or other experimental model systems, and extrapolated to humans and other animals. Methods for estimating the LD_{50} of compounds in humans and other animals are well-known in the art. A composition, and any component within it, might have an LD_{50} value in rats of greater than 100 g/kg, greater than 50g/kg, greater than 20 g/kg, greater than 10 g/kg, greater than 5 g/kg, greater than 2 g/kg, greater than 1 g/kg, greater than 500 mg/kg, greater than 200 mg/kg, greater than 100 mg/kg, greater than 50 mg/kg, greater than 20 mg/kg, or greater than 10 mg/kg. In some embodiments, the therapeutic index of the composition (measured as the toxic dose for 50% of the population (TD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50})), is greater than 1, greater than 10, or greater than 100.

Preparation and Storage of Vaccines Formulations and Immunogenic Compositions

[0259] The immunogenic compositions described herein may be produced using a variety of techniques. For example, a polypeptide may be produced using recombinant DNA technology in a suitable host cell. A suitable host cell may be bacterial, yeast, mammalian, or other type of cell. The host cell may be modified to express an exogenous copy of one of the relevant polypeptide genes. Typically, the gene is operably linked to appropriate regulatory sequences such as a strong promoter and a polyadenylation sequence. In some embodiments, the promoter is inducible or repressible. Other regulatory sequences may provide for secretion or excretion of the polypeptide of interest or retention of the polypeptide of interest in the cytoplasm or in the membrane, depending on how one wishes to purify the polypeptide. The gene may be present on an extrachromosomal plasmid, or may be integrated into the host genome. One of skill in the art

will recognize that it is not necessary to use a nucleic acid 100% identical to the naturally-occurring sequence. Rather, some alterations to these sequences are tolerated and may be desirable. For instance, the nucleic acid may be altered to take advantage of the degeneracy of the genetic code such that the encoded polypeptide remains the same. In some embodiments, the gene is codon-optimized to improve expression in a particular host. The nucleic acid may be produced, for example, by PCR or by chemical synthesis.

[0260] Once a recombinant cell line has been produced, a polypeptide may be isolated from it. The isolation may be accomplished, for example, by affinity purification techniques or by physical separation techniques (*e.g.*, a size column).

[0261] In a further aspect of the present disclosure, there is provided a method of manufacture comprising mixing one or more polypeptides or an immunogenic fragment or variant thereof with a carrier and/or an adjuvant. In some embodiments, the adjuvant is one that stimulates a T_H1 cell response.

[0262] In some embodiments, antigens for inclusion in compositions of the invention may be produced in cell culture. One method comprises providing one or more mammalian expression vectors and cloning nucleotides encoding two or more polypeptides selected from polypeptides having an amino acid sequence of any one of SEQ ID NOS: 1-38, 135, 136, 138 or 139, then expressing and isolating the polypeptides.

[0263] In some embodiments, nucleic acids for inclusion in compositions of the invention may be produced by replication in a bacterial host such as *E. coli* and purified by standard RNA or DNA purification methods.

[0264] The immunogenic polypeptides described herein, and nucleic acid compositions that express the polypeptides, can be packaged in packs, dispenser devices, and kits for administering nucleic acid compositions to a mammal. For example, packs or dispenser devices that contain one or more unit dosage forms are provided. Typically, instructions for administration of the compounds will be provided with the packaging, along with a suitable indication on the label that the compound is suitable for treatment of an indicated condition, such as those disclosed herein.

Combination Therapy

[0265] Combination therapy refers to those situations in which a subject or population of subjects is simultaneously exposed to two or more therapeutic regimens (*e.g.*, two or more therapeutic agents such as antiviral therapy and an immunogenic composition). In some embodiments, the two or more therapies may be administered simultaneously (e.g., concurrently). In some embodiments, such therapies may be administered sequentially (*e.g.*, all "doses" of a first regimen are administered prior to administration of any doses of a second regimen).

[0266] The present disclosure teaches methods of treating herpes using two or more therapeutic regimens, such as antiviral therapy and immunogenic composition, administered in overlapping dosing regimens. In some embodiments, a dosing regimen for one or more agents may comprise a plurality of "cycles" of doses administered according to a specified pattern. In some embodiments, specified pattern of administration for antiviral therapy is daily, about every other day, about every 3 days, about every 4 days, about every 5 days, about every 6 days, about every 7 days (e.g., weekly), about every 14 days (e.g., biweekly), about every 21 days, about every 28 days, about every 35 days, about every 42 days, about every 49 days, about every 2 months, about every 6 months or longer. In some embodiments, antiviral therapy is administered daily. In some embodiments, herpes is genital herpes.

[0267] In some embodiments, specified pattern of administration for immunogenic composition is at about every 7 days, about every 14 days, about every 21 days, about every 28 days, about every 35 days, about every 42 days, about every 49 days, about every 56 days or longer. In some embodiments, immunogenic composition is administered in at least one dose, at least two doses, at least three doses, at least four doses, at least 5 doses or more. In some embodiments, immunogenic composition is administered on about day 1, on about day 22 and on about day 43 of a therapeutic regimen. In some embodiments, a therapeutic regimen comprises daily administration of antiviral therapy. In some embodiments, a therapeutic regimen comprises daily administration of antiviral therapy beginning at least 14 days prior to administration of vaccine formulation wherein the vaccine formulation is administered in three doses about 21 days apart.

[0268] In some embodiments, the immunogenic composition comprises an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain, and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide. In some embodiments, immunogenic composition comprises about 10 μg, 20 μg, 30 μg, 60 μg, or 100 μg of each of a gD2 polypeptide and a ICP4 polypeptide and/or about 25 μg, 50 μg or 75 μg of adjuvant. In some embodiments, immunogenic composition comprises about 60 μg of the gD2 polypeptide, about 60 μg of the ICP4 polypeptide and about 50 μg of adjuvant.

[0269] In some embodiments, antiviral therapy is selected from the group consisting of famciclovir, valacyclovir, acyclovir, penciclovir, trifluridine, acyclovir in combination with hydrocortisone, helicase-primase inhibitors (e.g., amenamevir and pritelivir) and combinations thereof. In some embodiments, antiviral therapy is valacyclovir. In some embodiments, a subject or population of subjects receives about 500 mg to about 1 g of antiviral therapy per dose.

[0270] In some embodiments, "administration" of combination therapy may involve administration of one or more agents or modalities to a subject receiving the other agents or modalities in the combination. For clarity, combination therapy does not require that individual agents be administered together in a single composition (or even necessarily at the same time), although in some embodiments, two or more agents, or active moieties thereof, may be administered together in a combination composition, or even in a combination compound (*e.g.*, as part of a single chemical complex or covalent entity).

[0271] In some embodiments, immunogenic composition and/or antiviral therapy treats infection by HSV-1, HSV-2, or HSV-1 and HSV-2 in a subject or population of subjects.

Patient Populations

[0272] Among other things, the present disclosure includes methods of treating herpes infection in certain patient populations using combination therapy comprising an immunogenic composition described herein and an antiviral therapy described herein. In some embodiments, herpes is genital herpes. In some embodiments, a subject or subjects use contraception for 28

days before and 90 days after treatment with the immunogenic composition. In some embodiments, a subject or a population of subjects is male. In some embodiments, a subject or population of subjects is female. In some embodiments, a subject or population of subjects is non-pregnant female. In some embodiments, a subject or population of subjects is 10, 11, 12, 13, 14, 15, 16, or 17 years of old. In some embodiments, a subject or population of subjects is at least 18 years old and less than 51 years old. In some embodiments, a subject or population of subjects is 51 years or older.

[0273] In some embodiments, a subject or a population of subjects has been diagnosed with genital herpes infection for greater than 1 year. In some embodiments, diagnosis of genital herpes infection comprises Western blot analysis for one or more HSV-2 antigens; PCR (e.g., type-specific PCR); viral culture (e.g., type-specific viral culture); or compatible clinical history and positive HerpeSelect® 2 enzyme-linked immunosorbent assay IgG with an index value >3.5 or a positive LIAISON® HSV-2 Type Specific IgG.

[0274] In some embodiments, the immunogenic composition is administered to subjects or populations of subjects that have been receiving antiviral therapy. In some embodiments, antiviral therapy is valacyclovir, acyclovir or famciclovir. In some embodiments, a subject or population of subjects has been taking a stable dose of antiviral therapy for 6 or more months prior to administration of a immunogenic composition. In some embodiments, a subject or population of subjects has had at least one outbreak of genital herpes within 6 months of administration of a immunogenic composition. In some embodiments, a subject or population of subjects has been taking a stable dose of antiviral therapy for 6 or more months and has had at least one outbreak of genital herpes within 6 months of administration of a vaccine formulation. In some embodiments, a stable dose of antiviral is 500 mg per day or 1 g per day.

[0275] In some embodiments, the immunogenic composition is administered to subjects or populations of subjects that have not been receiving antiviral therapy. In some embodiments, a subject or population of subjects has been taking a stable dose of antiviral therapy for about 14 days prior to administration of a immunogenic composition. In some embodiments, a subject or population of subjects has had greater than 5 outbreaks of genital herpes within 12 months of

administration of a immunogenic composition. In some embodiments, a subject or population of subjects has been taking a stable dose of antiviral therapy of about 14 days and has had greater than 5 outbreaks of genital herpes within 12 months of administration of a immunogenic composition. In some embodiments, a stable dose of antiviral therapy is 500 mg once a day or 1 g once a day.

[0276] In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition is not receiving therapy comprising tenofovir, lysine, a supplement or medication, other than valacyclovir, e.g., a therapy known to or purported to affect herpes outbreak frequency or intensity. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition does not have a history of ocular herpes infection, herpes-related erythema multiforme, herpes meningitis or herpes encephalitis. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition does not have active genital HSV-2 lesions.

[0277] In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition is not immunocompromised. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition is not receiving systemic immunosuppressive medication. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition does not have an autoimmune disease. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition has not previously had an autoimmune disease. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition does not have HIV, hepatitis B or hepatitis C.

[0278] In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition does not have history of hypersensitivity to any component of a vaccine formulation. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition does not have a clinically significant laboratory abnormality except for (i) creatinine kinase in subjects with an identified exercise regimen and hepatic and renal enzyme levels within normal limits or (ii) isolated Grade 2 unconjugated bilirubin in fasting subjects with a history of Gilbert's syndrome.

[0279] In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition has not received any other vaccine containing an HSV-2 antigen. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition has not received an investigational product within 30 days prior to the first dose of immunogenic composition. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition has not received a blood product within 90 days prior to a first dose of vaccine formulation. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition has not received a live vaccine within 28 days prior to a first dose of vaccine formulation. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition has not received any other vaccine within 14 days prior to a first dose of vaccine formulation. In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition has received any other vaccine from the first dose until 28 days after a third dose.

[0280] In some embodiments, a subject or population of subjects treated with antiviral therapy and immunogenic composition is not pregnant or nursing.

Efficacy of Combination Therapies

[0281] Among other things, the present disclosure includes methods of treating herpes infection using combination therapy comprising immunogenic composition described herein and antiviral therapy so that efficacy of immunogenic composition and/or antiviral therapy is improved in a subject or population of subjects over a specified time period relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy, or receiving neither immunogenic composition or antiviral therapy. In some embodiments, antiviral therapy is administered to a subject or population of subjects receiving immunogenic composition. In some embodiments, immunogenic composition is administered to a subject or population of subjects receiving antiviral therapy. .

[0282] In some embodiments, combined administration of an immunogenic composition described herein and an antiviral therapy described herein results in an improvement in a disease

or disorder described herein or a symptom thereof to an extent that is greater than one produced by either the immunogenic composition or the antiviral therapy alone. The difference between the combined effect and the effect of the immunogenic composition or antiviral therapy alone can be a statistically significant difference. In some embodiments, the combined result is synergistic.

[0283] In some embodiments, combined administration of immunogenic composition and antiviral therapy allows administration of the antiviral therapy at a reduced dose, at a reduced number of doses, and/or at a reduced frequency of dosage compared to a standard dosing regimen approved for the antiviral therapy, such as an approved regimen for an antiviral therapy described herein. In some embodiments, combined administration of immunogenic composition and the antiviral therapy allows administration of the immunogenic composition at a reduced dose, at a reduced number of doses, and/or at a reduced frequency of dosage compared to an effective dosing regimen for the immunogenic composition.

[0284] In some embodiments, antiviral therapy is selected from the group consisting of famciclovir, valacyclovir, acyclovir and combinations thereof. In some embodiments, antiviral therapy is valacyclovir. In some embodiments, subjects receive about 500 mg to about 1 g of antiviral therapy per dose. In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is assessed at, at least 3 months, 6 months, 12 months, 18 months, 24 months, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years after administration of therapy. In some embodiments, efficacy of immunogenic composition and/or efficacy of antiviral therapy is assessed at least 6 months after administration of therapy.

[0285] In some embodiments, efficacy of immunogenic composition and/or antiviral formulation is measured or indicated by a genital herpes recurrence-free period relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, efficacy of immunogenic composition and/or antiviral formulation is measured or indicated by increased time to first herpes recurrence relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or

indicated by increased time to next herpes recurrence relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy.

[0286] In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreased genital herpes lesion rate relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreased genital herpes lesion frequency relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreased genital herpes lesion duration relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy.

[0287] In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreased rate of genital herpes outbreaks relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreased anogenital HSV shedding rate relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreased anogenital HSV shedding magnitude relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, viral shedding is measured is by real-time quantitative polymerase chain reaction (PCR).

[0288] In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreased or no increase of antiviral (e.g.,valacyclovir) dose relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy.

[0289] In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decrease of one or more herpes signs or symptoms relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy.

In some embodiments, a decrease in one or more herpes signs or symptoms is a decrease in the percentage of days with herpes-related signs or symptoms and/or a decrease in the magnitude of herpes-related signs or symptoms.

[0290] In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by increased health-related quality of life relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, health related quality of life is measured by the EuroQoL-5 Domains-5 Levels (EQ-5D-5L) questionnaire. In some embodiments, a subject or population of subjects completes the EQ-5D-5L questionnaire when not experiencing a genital herpes outbreak and or/on about each day of an outbreak.

[0291] In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreasing time to lesion healing relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreasing time to cessation of pain relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by decreasing rate of symptomatic acquisition of herpes in susceptible partners relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy.

[0292] In some embodiments, efficacy of immunogenic composition and/or antiviral therapy is measured or indicated by increase in humoral response and/or an increase in cellular response relative to a subject or population of subjects receiving only immunogenic composition or antiviral therapy. In some embodiments, increase in humoral response is measured or indicated by an increase in magnitude of response or fold rise from baseline of HSV-2 immunoglobulin G (IgG) levels and/or of HSV-2 neutralizing antibody levels. In some embodiments, baseline is a value, level, amount or quantity measured or indicated in a subject with herpes prior to administration of antiviral therapy and/or immunogenic composition. In some embodiments, baseline is a value, level, amount or quantity measured or indicated in a population of subjects with herpes prior to administration of antiviral therapy and/or

immunogenic composition. In some embodiments, baseline is a value, level, amount or quantity measured or indicated in a subject or population of subjects without herpes.

[0293] In some embodiments, increase in humoral response is indicated by a 4-fold or greater rise in IgG titer from baseline. In some embodiments, increase in humoral response is indicated by a 2-fold or greater rise in 50% neutralizing antibody titer from baseline. In some embodiments, cellular response is an increase in secretion of granzyme B (GrB) levels. In some embodiments, increase in cellular response is measured or indicated by increase in magnitude of response or fold rise from baseline of granzyme B (GrB) levels. In some embodiments, cellular response is an increase in IFNγ secretion from T cells.

[0294] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described herein.

[0295] The disclosure is further illustrated by the following examples. The examples are provided for illustrative purposes only. They are not to be construed as limiting the scope or content of the disclosure in any way.

EXEMPLIFICATION

Example 1: GEN-003-004 Clinical Study: A Randomized, Placebo-controlled, Double-blind Study to Assess the Efficacy and Safety of GEN-003 in Subjects with Genital HSV-2 Infection taking Valacyclovir Suppressive Therapy

Formulations

[0296] GEN-003 is an HSV-2 protein subunit vaccine consisting of two recombinant T-cell antigens (GB208 and GB217), Matrix-M2 adjuvant (M2) and diluent (0.9% normal saline). GB208 is an approximately 39 kDa T-cell antigen and internal fragment of the immediate early protein ICP4. ICP4 was identified as one of the most frequent proteins recognized by the T-cells of immune seronegative subjects studied by AnTigen Lead Acquisition System (ATLAS^{TM}), suggesting its potential role in control of viral replication and utility as a vaccine candidate. GB217 is a B-cell antigen and a recombinant version of the glycoprotein D, or gD, modified by deletion of the transmembrane region. This surface glycoprotein is a target of HSV-2 neutralizing antibodies and of T-cell responses. M2 is an immune stimulating complex-based adjuvant containing saponin fractions purified from fractionated *Quillaja saponins (soapbark tree)* bark, phosphatidylcholine, and cholesterol.

[0297] Summaries of the nonclinical pharmacology and toxicology studies are provided below.

Nonclinical Models of Immunogenicity and Efficacy

[0298] Immune responses to components of GEN-003 were evaluated in mice and monkeys. The study results indicated that GB208 and GB217 prime potent and functional T-cell and B-cell responses, including HSV-2 neutralizing antibodies, when administered with M2.

[0299] In a guinea pig model of vaginal HSV-2 infection, GEN-003 induced increases in GB208- and GB217-specific immunoglobulin G (IgG) titer and HSV-2 neutralizing antibodies (Skoberne et al 2013). The post-treatment mean number of days with genital HSV-2 lesions was reduced among animals receiving GEN-003 compared to

those in the placebo group. In this model, HSV-2 infected animals administered GB208 with M2 or GB204 (a form of GB217) with M2 had significant reductions in the number of days of viral shedding compared to animals administered placebo. No viral shedding was observed in 33% of animals administered GB204 and 50% of the animals administered GB208.

Nonclinical Toxicology Studies

[0300] Repeat-dose toxicology studies of GEN-003 antigens and M2 were performed in accordance with Good Laboratory Practice in mice, rabbits, and monkeys, and a local tolerance study was performed in rabbits. No safety signals believed to be relevant to potential risks to humans receiving GEN-003 were identified.

Clinical Trials of GEN-003

[0301] Two clinical trials of GEN-003 have been completed, and 3 trials are ongoing. Summaries of four trials are provided below.

GEN-003-001: A Phase I/IIa, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Study of the Safety and Immunogenicity of a HSV-2 Vaccine Containing Matrix M-2 Adjuvant in Individuals with Documented HSV-2 Genital Infection

[0302] Subjects aged 18 to 50 years with documented diagnosis of genital HSV-2 infection for >1 year but who were otherwise healthy were enrolled sequentially into 1 of 3 dose cohorts defined by the antigen dose (10, 30, or 100 μg for each of the 2 protein antigens) and randomized within each cohort in a ratio of 3:1:1 to receive 3 intramuscular (IM) doses of GEN-003 antigens with M2, GEN-003 antigens without M2, or placebo at intervals of 21 days. The study is complete; 143 subjects were enrolled.

[0303] GEN-003 antigens with or without M2 exhibited an acceptable safety and tolerability profile for use as a therapeutic vaccine. Five serious adverse events (SAEs) in 5 subjects (femur fracture, suicide attempt, complicated migraine, myocardial infraction, abortion spontaneous) were reported during the course of the study, and none was considered associated with treatment. No adverse events of special interest (AESIs) were reported.

[0304] GEN-003 antigens generated a reduction in HSV-2 shedding rates that was maintained for at least 6 months after treatment, and the greatest reduction was achieved in the adjuvanted 30 µg dose group. No reduction in HSV-2 shedding occurred in the absence of M2. Thirty (30) µg GEN-003 reduced lesion rates for at least 6 months post-treatment. One hundred (100) µg GEN-003 also reduced HSV-2 shedding and lesion rates (number of days with lesions divided by the 28-day duration of the swab collection period) but less durably.

[0305] GEN-003 antigens elicited strong and durable antibody and T-cell immune responses to both vaccine-specific antigens and production of HSV-2 neutralizing antibodies at all doses. The addition of M2 augmented these responses.

GEN-003-002: A Randomized, Double-Blind, Factorial Study to Compare the Safety and Efficacy of Varying Combinations of GEN-003 and Matrix- M2 in Subjects with Genital HSV-2 Infection

[0306] Subjects aged 18 to 50 years with documented diagnosis of genital HSV-2 infection for >1 year were randomized in equal proportions to receive 3 IM doses of 1 of the following formulations at intervals of 21 days:

- 30 µg each GEN-003 antigen with 25 µg M2
- 30 µg each GEN-003 antigen with 50 µg M2
- 30 µg each GEN-003 antigen with 75 µg M2
- 60 µg each GEN-003 antigen with 25 µg M2
- 60 µg each GEN-003 antigen with 50 µg M2
- 60 µg each GEN-003 antigen with 75 µg M2
- Placebo

[0307] The study is complete; 310 subjects were enrolled.

[0308] Reduction in anogenital HSV-2 shedding was observed in all active treatment combinations immediately after the last dose and persisted to 12 months after the last dose. The most effective dose combinations (60 µg each GEN-003 antigen with 50 µg M2 and 60 µg each GEN-003 antigen with 75 µg M2) also reduced HSV-2 lesion rates (the % of days with subject-recorded HSV-2 lesions in a 28-day observation period). Risk ratios (95% confidence intervals [CIs]) compared to Baseline were 0.35 (0.18, 0.71; $P = 0.0033$) and 0.53 (0.31, 0.89; $P =$

0.0165), respectively. These 2 doses are currently being further evaluated in Study GEN-003-003.

[0309] GEN-003 exhibited an acceptable safety and tolerability profile for use as a therapeutic vaccine in all dose combinations. Ten SAEs in 8 subjects (femur facture, myocardial infarction, viral syndrome, post lumbar puncture syndrome, pyelonephritis, diverticulitis, bipolar disorder exacerbation [2 events], cholecystitis, and overdose) were reported during the course of the study, and none was considered associated with treatment. All of the SAEs resolved, and only one event (femur fracture) had sequelae. No AESIs were reported.

[0310] Six subjects discontinued dosing because of an adverse event (AE) or laboratory abnormality and 3 subjects discontinued because of a local reaction or systemic event, with no differences noted across the treatment groups (no more than 2 in any group). The frequency of Grade 3 AEs within 7 days of any dose was 4% for subjects who received placebo and ranged from 20% to 43% among active dose groups. The most common systemic events were fatigue and muscle aches, which were generally related to adjuvant dose

GEN-003-002a: Rollover Trial for Placebo Subjects Previously Enrolled into GEN-003-002 - A Randomized, Double-Blind, Factorial Study to Compare the Safety and Efficacy of Varying Combinations of GEN-003 and Matrix-M2 in Subjects with Genital HSV-2 Infection

[0311] Subjects who received placebo in Study GEN-003-002 were offered enrollment in this open-label study of the same active dose combinations given in that study. A total of 37 subjects were enrolled and have completed the dosing period, and the study is ongoing.

[0312] No SAEs or AESIs have been reported.

GEN-003-003: A Randomized, Double-blind Study to Evaluate a New Formulation of GEN-003 in Subjects with Genital HSV-2 Infection

[0313] Subjects aged 18 to 50 with documented diagnosis of genital HSV-2 infection for >1 year were randomized in a 1:1:1 ratio to receive 3 IM doses of 1 of the following formulations at intervals of 21 days:

- GEN-003: 60 μg each antigen and 50 μg M2

- GEN-003: 60 µg each antigen and 75 µg M2
- Placebo (normal saline)

[0314] A total of 131 subjects were enrolled and have completed the dosing period. Safety data are being reviewed by an independent Data Monitoring Committee (DMC) throughout the study. As of June 13, 2016, the DMC has recommended continuing the trial as planned. Two SAEs in 2 subjects have been reported (meningitis, ductal carcinoma in situ), and neither were considered associated with treatment. No AESIs have been reported.

GEN-003-004 Study Rationale

[0315] The only currently approved medications for the prevention of outbreaks caused by genital HSV-2 are antiviral medications (Valtrex 2013, Famvir 2013). The endpoint by which these medications were studied and approved was the proportion of subjects initiating therapy who remained HSV-2 recurrence-free at 6 months or 12 months. For valacyclovir (the most commonly prescribed medication for recurrent genital HSV-2), the proportion of patients who remained recurrence-free at 6 months was 55% (compared to 7% for patients who received placebo) and at 12 months was 34% (compared to 4% for patients who received placebo). Thus, oral antiviral therapy only partially suppresses the recurrences of genital HSV-2.

[0316] In addition, antiviral suppressive therapy does not completely eliminate viral shedding (Johnston et al., Lancet. (2012) 379:641–7) and reduces transmission risk by only 48% (Corey et al., N Engl J Med. (2004) 350:11-20 2004). GEN-003 reduces viral shedding by over 50% and combination with suppressive therapy may show additional activity compared to valacyclovir alone, possibly because of the different mechanisms of action.

[0317] This study evaluates the combined activity of an optimized dose of GEN-003 in combination with valacyclovir suppressive therapy compared to valacyclovir suppressive therapy alone.

Objectives

[0318] The primary objective of the study is to compare the effect of GEN-003 versus placebo administered to subjects taking valacyclovir suppressive therapy to the proportion of

subjects who are genital HSV-2 recurrence-free at 6 months after the Last Dose and 12 months after the Last Dose. A secondary objective of the study is to compare the effect of GEN-003 versus placebo administered to subjects taking valacyclovir suppressive therapy on clinical outcomes. The clinical outcomes include:

- Proportion of subjects who are genital HSV-2 recurrence-free at 6 months after Dose 1 and 12 months after Dose 1;
- Time to first genital HSV-2 recurrence after Dose 1 and after Last Dose;
- Time to next genital HSV-2 recurrence after Dose 1 and after Last Dose;
- Genital HSV-2 lesion rate;
- Rate of genital HSV-2 outbreaks;
- Duration of genital HSV-2 outbreaks;
- Anogenital HSV-2 shedding rate and magnitude; and
- Number of subjects who increase valacyclovir dose.

[0319] Another secondary objective of the study is to evaluate safety and tolerability of GEN-003 in subjects taking valacyclovir suppressive therapy. One exploratory objective of the study is to compare immune responses to GEN-003 versus placebo in subjects taking valacyclovir suppressive therapy. Another exploratory objective of the study is to compare duration, severity, and bother of genital herpes symptoms in subjects taking GEN-003 versus placebo and valacyclovir suppressive therapy. A third exploratory objective of the study is to assess health-related quality of life in the presence and absence of a genital herpes recurrence as measured by the EuroQol – 5 Domains – 5 Levels (EQ-5D-5L) questionnaire.

Study Design

[0320] This study is a randomized, double-blind, placebo-controlled clinical trial of GEN-003 in subjects taking valacyclovir suppressive therapy. Subjects aged 18 to 50 years with documented diagnosis of genital HSV-2 infection for >1 year and ≥6 months of use of a stable dose of valacyclovir suppressive therapy or willingness to start valacyclovir suppressive therapy are eligible for screening.

[0321] Subjects who pass initial screening begin the 14-day Baseline Period comprising once daily administration of valacyclovir, reporting use via a daily electronic tool of genital herpes lesions, genital herpes symptoms, and valacyclovir use; daily completion of the EQ-5D-5L questionnaire, and a daily single dose of valacyclovir. Subjects taking valacyclovir suppressive therapy before the Baseline Period continue using the same dose of valacyclovir (500 mg or 1 g once a day). Subjects initiating valacyclovir suppressive therapy during the Baseline Period take 500 mg once a day. Immediately after successful completion of the Baseline Period (e.g., entered data into the daily electronic reporting tool, took valacyclovir, and completed the EQ-5D-5L on ≥11 of 14 days), subjects who meet all inclusion and no exclusion criteria are randomized. Randomization is stratified by prior duration of valacyclovir suppressive therapy use (≥6 months or initiated at Baseline Period only).

[0322] Up to 300 subjects are randomized in a 1:1 ratio to receive 3 IM doses of GEN-003 (60 μg of each antigen and 50 μg of M2) or placebo at intervals of 21 days (Days 1, 22, and 43). The subject remains on the same valacyclovir dose (500 mg once a day or 1 g once a day) through Day 71/Month 1. After Day 71/Month 1, a subject taking 500 mg once a day increases the dose to 1 g once a day if he/she experiences a genital HSV-2 outbreak and the Investigator agrees. Subjects continue to take valacyclovir once a day until the end of the study.

[0323] Subjects continue to use the daily electronic tool for reporting of genital herpes lesions, genital herpes symptoms, and valacyclovir use until the end of the study. The subject reports to the investigational site the first time he/she notes the presence of genital lesions, and a clinician examines the subject to confirm the presence of genital lesions consistent with HSV-2 and, if present, collects a lesion swab sample for detection of HSV-2 DNA. Subjects complete the EQ-5D-5L on each day of every outbreak during the study.

[0324] Subjects collect anogenital swabs for measurement of HSV-2 shedding twice a day for 28-day periods immediately after Dose 3 (Days 43 to 71), from Month 5 to 6, and from Month 11 to 12. Samples are analyzed for HSV-2 DNA by real-time quantitative PCR.

[0325] A serum sample is collected from each subject for evaluation of humoral responses before Dose 1, 7 days after Dose 3 (Day 50), 28 days after Dose 3 (Day 71/Month 1),

and at Months 6 and 12. HSV-2 IgG is measured by enzyme-linked immunosorbent assay, and HSV-2 neutralizing antibody is measured by a colorimetric assay. At selected investigational sites, a whole blood sample is collected and processed to isolate peripheral blood mononuclear cells (PBMCs) for evaluation of cellular responses before Dose 1, 7 days after Doses 1 and 3 (Days 8 and 50), and at Months 6 and 12. Secretion of granzyme B (GrB) specific to the vaccine-specific antigens is measured by GrB enzyme-linked immunosorbent spot assay (ELISPOT).

[0326] Local reactions and systemic events are recorded 1 hour postdose at the investigational site and for the first 7 days after each dose on the Diary Card; if any event is ongoing after the 7-day diary reporting period, it is followed until resolution. All AEs and concomitant medications are recorded from Day 1 to Day 71/Month 1. After Day 71/Month 1 to the end of the study, only SAEs, AESIs, antivirals (other than valacyclovir), and vaccines are recorded. Symptom-driven physical examinations are performed at all visits from Day 1 to Day 71/Month 1 and at Months 6 and 12, and vital signs are measured at all visits from Day 1 to Day 71/Month 1, including before and 1 hour after each GEN-003/placebo dose. Hematology, serum chemistry, and urine samples are collected 7 days after each GEN-003/placebo dose (Days 8, 29, and 5) and 28 days after Dose 3 (Day 71/Month 1).

[0327] After Day 71/Month 1, the subjects visit the investigational site monthly for check of valacyclovir supply, review of daily electronic reporting tool data, collection of any completed EQ-5D-5L questionnaires, check of EQ-5D-5L questionnaire supply, and assessment of SAEs, AESIs, and antiviral medication and vaccine use.

[0328] A DMC reviews safety data at intervals of a minimum of 3 months until all subjects have completed the GEN-003/placebo dosing period. Any additional meetings and the specific safety monitoring plan are detailed in the DMC charter.

[0329] An interim analysis is conducted after all subjects have completed the Month 6 visit.

Study Population

[0330] The study population consists of patients with documented HSV-2 infection who have been taking valacyclovir suppressive therapy at a stable dose (either 500 mg or 1 g) once a

day for at least 6 months or are willing to start valacyclovir suppressive therapy. Subjects who have been taking valacyclovir suppressive therapy have had at least 1 outbreak in the past 6 months. Subjects who start valacyclovir suppressive therapy for the study have had >5 outbreaks in the past 12 months. This study population represents a target population likely to benefit from a therapeutic HSV-2 vaccine.

Dosing Regimen

Among the antigen and adjuvant combinations tested in Study GEN-003-002, the largest reductions in HSV-2 shedding were observed in subjects who received 60 μg of each antigen with 50 or 75 μg of M2. The GEN-003 dose for this study is 60 μg of each antigen with 50 or 75 μg of M2.

Stratification

[0331] Subjects taking a stable dose (500 mg once a day or 1 g once a day) of valacyclovir suppressive therapy (for ≥6 months) are enrolled only if they have had an outbreak of genital HSV-2 and thus have demonstrated incomplete HSV-2 control regardless of valacyclovir dose. Consequently, there is no need to stratify subjects by dose (all subjects newly initiating valacyclovir take 500 mg once a day). Subjects are, however, stratified by prior duration of suppressive therapy use: (≥6 months or initiated at Baseline Period only). This stratification minimizes bias caused by potential variability in subject responses to antiviral suppression and uncertainty in long-term effectiveness of antiviral suppression.

Efficiacy Endpoints

[0332] Proportion of subjects recurrence-free at 6 and 12 months post-treatment is a clinically important measure of efficacy that has been used as the primary efficacy measure for currently available treatments for HSV-2 genital infection (Valtrex 2013, Famvir 2013). Although both the proportion of subjects recurrence-free and time to first HSV-2 recurrence are important measures of clinical efficacy, the proportion of subjects recurrence-free fails to account for vaccine effect in prolonging the period between HSV-2 recurrences and time to HSV-2 recurrence after the first recurrence. Time to next recurrence accounts for the vaccine effect over the course of the 6-or 12-month period by measuring and averaging the intervals

between all recurrences, thus providing a more complete picture of vaccine effect over the observed time period.

[0333] Viral shedding is a direct measurement of antiviral activity that has been used in previous studies of both vaccines and antiviral medications for genital HSV-2. It is an objective measure of antiviral activity against HSV-2.

[0334] Subjects report daily severity and bother for 5 HSV-2-related symptoms (itch, pain, burning sensation, tingling, irritation) if present. The purpose of collecting patient-reported assessment of symptoms is to identify episodes of HSV-2-related symptoms that may or may not coincide with patient-reported presence of genital lesions (e.g., prodrome). In addition, GEN-003 may reduce the severity of symptoms related to recurrent outbreaks of genital HSV-2.

[0335] The EQ-5D-5L is a self-administered questionnaire designed as a standardized measure of health-related quality of life and has been used to study a wide range of medical conditions.

Study Duration

[0336] The total duration of enrollment is 6 months; the actual duration of enrollment may be longer. The duration of each subject's participation (including Screening) is up to 14.5 months. Thus, the study lasts approximately 21 months.

Subject Population

Inclusion Criteria

[0337] Subjects who participate in the study meet the following inclusion criteria:

1. males and nonpregnant females, ages 18 to 50 years inclusive;
2. medical history consistent with genital herpes for > 1 year;

   taking valacyclovir suppressive therapy at a stable dose (either 500 mg or 1 g) once a day for at least 6 months before the Baseline Period AND history of at least 1 outbreak in the 6 months before the Baseline Period

   OR

willing to start 500 mg valacyclovir suppressive therapy at 500 mg once a day for the Baseline Period AND history of >5 outbreaks in the 12 months before the Baseline Period;

3. diagnosis of genital HSV-2 infection supported by **ONE** of the following documented in the medical history or performed at Screening:

a) Western blot for HSV-2;

b) type-specific PCR **OR** viral culture;

c) compatible clinical history **AND**;

i) positive HerpeSelect® 2 enzyme-linked immunosorbent assay (ELISA) IgG with an index value >3.5 **OR**;

ii) positive LIAISON® HSV-2 Type Specific IgG;

4. completion of the daily electronic reporting tool, took once daily valacyclovir, and completed the EQ-5D-5L on at least 11 of 14 days in the Baseline Period;

5. willing and able to provide written informed consent;

6. willing to perform and comply with all study procedures including attending clinic visits as scheduled; and

7. willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, intrauterine device (IUD), or use of a spermicide combined with a barrier method (e.g., condom, diaphragm) for 28 days before and 90 days after receiving the investigational product (IP).

Exclusion Criteria

[0338] Subjects who meet any one of the following criteria are excluded from participation in the study:

1. use of tenofovir, lysine, or medication (other than valacyclovir) or supplement known or purported to affect HSV outbreak frequency or intensity within 14 days prior to Dose 1 of GEN-003/placebo;

2. history of any form of ocular HSV infection, HSV-related erythema multiforme, or herpes meningitis or encephalitis;

3. have active genital HSV-2 lesions (the subject may enter the study once lesions have re-epithelialized);

4. immunocompromised individuals, including those receiving any type of systemic immunosuppressive medication within 30 days prior to Dose 1 of GEN-003/placebo;

5. presence or history of autoimmune disease (see, Table 3), regardless of current treatment;

6. current infection with HIV or hepatitis B or C virus;

7. clinically significant laboratory abnormality or a value ≥Grade 2 except for (i) Grade 2 creatinine kinase in an individual with an identified exercise regimen and hepatic and renal enzyme levels within normal limits or (ii) isolated Grade 2 unconjugated bilirubin in fasting subject with history of Gilbert's syndrome;

8. history of hypersensitivity to any component of the vaccine;

9. prior receipt of GEN-003 or another vaccine containing HSV-2 antigens;

10. receipt of any IP within 30 days prior to Dose 1 of GEN-003/placebo;

11. receipt of any blood product within 90 days prior to Dose 1 of GEN-003/placebo;

12. receipt of a live vaccine within 28 days prior to or any other vaccine within 14 days prior to Dose 1 of GEN-003/placebo;

13. planned use of any vaccine from Dose 1 of GEN-003/placebo to 28 days after Dose 3 of GEN-003/placebo;

14. pregnant or nursing women;

15. history of drug or alcohol abuse that, in the opinion of the Investigator, would interfere with the subject's ability to comply with the requirements of the study;

16. other active, uncontrolled comorbidities that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with the study requirements; or

17. changes to medication used to manage an underlying comorbidity within 60 days prior to Dose 1 of GEN-003/placebo.

[0339] Table 3. Autoimmune Diseases

Gastrointestinal disorders • Celiac disease • Crohn's disease • Ulcerative colitis • Ulcerative proctitis
Liver disorders • Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis
Metabolic diseases • Addison's disease • Autoimmune thyroiditis (including Hashimoto thyroiditis) • Diabetes mellitus type I

• Grave's or Basedow's disease
Musculoskeletal disorders • Antisynthetase syndrome • Dermatomyositis • Juvenile chronic arthritis (including Still's disease) • Mixed connective tissue disorder • Polymyalgia rheumatic • Polymyositis • Psoriatic arthropathy • Relapsing polychondritis • Rheumatoid arthritis • Scleroderma (including diffuse systemic form and CREST syndrome) • Spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis) • Systemic lupus erythematosus • Systemic sclerosis
Neuroinflammatory disorders • Acute disseminated encephalomyelitis (including site specific variants: e.g., noninfectious encephalitis, encephalomyelitis, myelitis, and myeloradiculomyelitis) • Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy) • Guillain-Barre syndrome (including Miller Fisher syndrome and other variants) • Immune-mediated peripheral neuropathies and plexopathies (including chronic

inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and polyneuropathies associated with monoclonal gammopathy) • Multiple sclerosis • Narcolepsy • Optic neuritis • Transverse myelitis
Skin disorders • Alopecia areata • Autoimmune bullous skin diseases (including pemphigus, pemphigold, and dermatitis herpetiformis) • Cutaneous lupus erythematosus • Erythema nodosum • Morphoea • Lichen planus • Psoriasis • Sweet's syndrome • Vitiligo
Vasculitides • Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis) • Medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome [allergic granulomatous angiitis], Buerger's disease

[thromboangiitis obliterans], necrotizing vasculitis and antineutrophil cytoplasmic antibody positive vasculitis [type unspecified], Henoch- Schonlein purpura, Behcet's syndrome, and leukocytoclastic vasculitis)

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including immunoglobuiln A nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjogren's syndrome
- Stevens-Johnson syndrome
- Uveitis

Investigational Products

Formulation

[0340] GEN-003 consists of 2 recombinant antigens corresponding to 2 distinct HSV-2 proteins (GB208 and GB217) in combination with M2 and diluent. These components are detailed in Table 4.

Table 4: Composition of GEN-003

Ingredient	Description	Dose
GB208	Corresponds to a ~39 kDa internal fragment of the ICP4 protein	60 µg
GB217	A recombinant version of the glycoprotein gD modified by a deletion of the transmembrane region	60 µg
Matrix-M2 Adjuvant	An immune stimulating complex-based adjuvant containing saponin fractions purified from *Quillaja saponaria* (soapbark tree) bark, phosphatidylcholine, and cholesterol	50 µg
Diluent	0.9% normal saline	Not applicable

Packing and Labeling of Vaccine Formulation

[0341] GEN-003/placebo is prepared from the following 3 components before injection:

(1) GB208 and GB217 antigens in a lyophilized form are supplied in a 3 mL glass vial containing 125 µg, at a concentration of 0.25 mg/mL when reconstituted to a volume of 0.5 mL.

(2) M2 is supplied in a second 3 mL glass vial containing 0.75 mL of M2 at a concentration of 1 mg/mL.

(3) Normal saline (0.9% sodium chloride in water) from commercially available supply is supplied in a third vial for dilution of antigens to the desired concentration and for use as placebo.

[0342] The vaccine components are packaged and labeled as IPs in accordance with applicable legal and regulatory requirements.

Storage

[0343] The antigens and M2 are stored at 2°C to 8°C. The site must report excursions above 10°C to the Sponsor for an assessment of product quality. Normal saline is stored at ambient temperature.

Preparation and Administration

[0344] Preparation of GEN-003/placebo is performed by a designated unblinded site pharmacist (or otherwise qualified personnel) in accordance with the Pharmacy Manual provided by the Sponsor. Preparation requires approximately 30 minutes.

[0345] GEN-003/placebo is administered by trained study personnel. Each injection consists of a total volume of 0.5 mL administered IM to the deltoid muscle of either arm. Both 1.0-inch and 1.5-inch needles are provided. For obese subjects, a 1.5-inch needle is recommended.

Antiviral Therapy

[0346] Commericially available 500 mg valacyclovir tablets are supplied and provided to subjects in the original commerical packaging and lables as investigational products in accordance with applicable legal and regulatory requirements. Valacyclovir is stored at 15°C to 25°C (59°F to 77°F) in accordance with the Prescribing Information. Valacyclovir is dispensed at clinic visits as detailed in the Study Procedures Section. Valacyclovir is taken with or without food. Subjects are advised to maintain adequate hydration while taking valacyclovir.

Randomization and Dosing

[0347] Eligible subjects are randomized in a 1:1 ratio to receive 3 IM doses of GEN-003 (60 μg each antigen and 50 μg M2) or placebo at intervals of 21 days (Days 1, 22, and 43). Randomization is stratified by prior duration of valacyclovir suppressive therapy use (≥6 months or initiated at Baseline Period only).

[0348] Randomization is achieved using the randomization component of the electronic case report form (eCRF). After subject eligibility is confirmed on this form, the system sends an e-mail to the unblinded pharmacist (or otherwise qualified personnel) with instructions for accessing the treatment assignment.

[0349] The subject remains on the same valacyclovir dose (500 mg once a day or 1 g once a day) through Day 71/Month 1. After Day 71/Month 1, a subject taking 500 mg once a day increases the dose to 1 g once a day if he/she experiences a genital HSV-2 outbreak and the Investigator agrees.

Blinding and Unblinding

[0350] Investigators, subjects, and all study staff with direct subject contact are blinded to treatment assignment (GEN-003 vs placebo). A designated unblinded pharmacist (or otherwise qualified personnel) at each site prepares each dose. That individual has no contact with the subjects and minimize contact with other site study personnel.

[0351] Unblinding of treatment assignment is discouraged. In the event of a medical emergency, for which the identity of the treatment assignment is critical to the care of a subject, the Investigator calls the Medical Monitor to discuss. In the event that unblinding is deemed necessary, an unblinded statistician provides the treatment assignment to the Medical Monitor who provides the information to the Investigator. A decision to discontinue a subject from further IP administration is not a rationale for unblinding the treatment assignment

[0352] An unblinded statistician is available to the DMC and Medical Monitor and reviews interim analyses.

Investigational Product Accountability, Dispensing and Destruction

[0353] The Investigator (or designee) maintains an accurate record of the receipt of the GEN-003 components and valacyclovir as shipped by the Sponsor (or designee), including the date received. In addition, an accurate GEN-003/placebo disposition record is kept, specifying the amount administered to each subject, and an accurate valacyclovir disposition record is kept, specifying the amount dispensed to each subject and the dates of dispensation and return.

[0354] At the completion of the study, all unused IP supplies are returned to the Sponsor (or designee) or disposed of by the site in accordance with the Sponsor's (or designee's) written instructions.

Concomitant Medications

[0355] All concomitant medications (not including valacyclovir), including over-the-counter medications and supplements, are recorded in the eCRF from Dose 1 to Day 71/Month 1. Use of antivirals (other than valacyclovir) and vaccines is recorded from Screening through the end of the study.

Medications and Supplements with Anti-HSV Activity

[0356] Use of tenofovir (except for postexposure prophylaxis for HIV-1), lysine, or medication (other than valacyclovir) or supplement known or purported to affect HSV outbreak frequency or intensity is prohibited from 14 days before Dose 1 to the end of the study.

Topical Steroids and Antiviral Medications

[0357] Use of topical steroids or antiviral medication in the anogenital region is prohibited from 14 days before the beginning of each swab collection period to the end of the swab collection period.

Immunosuppressive Medications

[0358] Systemic immunosuppressive medications are prohibited from 30 days before Dose 1 to the end of the study.

Vaccines

[0359] Subjects do not receive a live vaccine within 28 days prior to Dose 1 or any other vaccine within 14 days prior to Dose 1. In addition, subjects do not receive any vaccine from Dose 1 to 28 days after the last dose of GEN-003/placebo. It is particularly important to reinforce this information if the subject is receiving GEN-003/placebo during the influenza season

Other Study Restrictions

[0360] There are no restrictions on fluid or food intake during the study. However, because of the large volume of blood drawn on days when PBMCs are obtained, subjects are well-hydrated. Subjects should also maintain hydration while taking valacyclovir. Subjects refrain from excessive physical activity for 48 hours before each study visit from Screening through Day 71/Month 1. Male and female subjects practice a highly effective method of contraception that includes, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, IUD, or use of spermicide combined with barrier method (e.g., condom, diaphragm) for 28 days before Dose 1 through 90 days after the last dose of GEN-003/placebo3. Subjects are advised that GEN-003 has not been proven to reduce the likelihood of transmission of HSV-2 infection to an uninfected sexual partner. Valacyclovir has been shown to reduce but not eliminate the risk of transmission. In addition, the efficacy of condoms for the prevention of HSV-2 infection is limited.

Treatment Compliance

[0361] To ensure compliance with the dosing regimen, all doses of GEN-003/placebo are administered by trained study personnel in the clinic who have been delegated that responsibility by the Investigator. Subjects report valacyclovir use via the daily electronic reporting tool and are required to return all bottles at each clinic visit. Clinic visits are conducted within the windows of the specified date.

Study Procedures

Definitions and Descriptions of Assessments and Procedures

[0362] **Complete physical examination** – Examination of the following systems: cardiovascular; dermatological; ear, nose, and throat; extremities; gastrointestinal; genitourinary; musculoskeletal; neurological ophthalmological; neurological; respiratory.

[0363] **Symptom-driven physical examination** – Brief, focused examination of the subject following medical history.

[0364] **Vital signs** – Temperature, heart rate, blood pressure. Heart rate and blood pressure are obtained after subject is seated for 5 minutes.

[0365] **Hematology** – Hemoglobin, red blood cell count, white blood cell count and differential, platelet count.

[0366] **Serum chemistry** – Alanine aminotransferase, aspartate aminotransferase, creatinine, creatine kinase, potassium, sodium, total bilirubin.

[0367] **Urinalysis** – Glucose, occult blood, protein.

[0368] **Serum/urine pregnancy tests** – For all women regardless of menopausal status other than those that have been surgically sterilized (by hysterotomy or bilateral tubal ligation).

[0369] **Anogenital swabs** – Subjects are provided with a swab kit (containing Swab Log, swabs, collection tubes, labels, and storage boxes) for the swab collection period. Subjects are instructed to collect anogenital swabs twice a day for 28-day periods. Subjects do not collect swabs for more than 28 days (e.g., more than 56 swabs).

[0370] **Swab Log** – Subjects are provided with a Swab Log for the swab collection period to indicate date and time of each swab collected.

[0371] **Genital herpes lesions** – Papules, pustules, vesicles, or ulcers, including those that have crusted. Symptoms of prodrome, redness, itchiness, or postinflammatory hyperpigmentation of re- epithelialized ulcers do not constitute the presence of lesions.

[0372] **Daily electronic reporting tool** – Each day subjects report the presence or absence of genital lesions, genital herpes symptoms, and valacyclovir use. In addition, if genital herpes symptoms are present, subjects also rate the severity and bother of the symptoms using the questions from the Genital Herpes Signs and Symptoms Diary. Data is entered daily. A subject receives a daily text reminder if data are entered for that day. The investigational site receives a weekly e-mail notification if a subject misses any data, and the site makes contact with the subject to promote compliance.

[0373] **First recurrence of HSV-2** –The subject returns to the investigational site within 72 hours (preferably within 24 to 48 hours) of the first time he/she notes the presence of new

genital lesions after Dose 1 for confirmation of lesions by the Investigator (or Subinvestigator) (see, Study Vaccine (GEN-003/Placebo) Dosing Period section).

[0374] **EQ-5D-5L** – Subjects completes the paper questionnaire each day during the Baseline Period and each day genital lesions are present.

[0375] **Reactogenicity** – Subjects are interviewed and examined at 1 hour after each dose and the following items is entered in the eCRF:

i) Local reactions: pain, tenderness, swelling, redness

ii) Systemic events: headache, chills, fatigue, nausea, vomiting, diarrhea, muscle aches

iii) Oral temperature

[0376] The subjects also record these items on a Diary Card for the first 7 days after each dose, and the information is entered in the eCRF.

[0377] **Diary Card** – Subjects are provided a Diary Card to record local reactions, systemic events, and oral temperature for the 7 days following each dose. If there are any events ongoing after the 7-day diary reporting period these events are followed until resolution and the stop date recorded. The Investigator (or Subinvestigator) review Diary Cards with the subject. Any changes or comments to the subject's Diary Card are made on the Diary Card and initialed and dated by the Investigator (or Subinvestigator). The Diary Card and the Investigator's (or Subinvestigator's) assessment serve as the source document. An event recorded on the Diary Card is recorded on the AE eCRF unless it meets the criteria of an SAE.

[0378] **AEs (including SAEs and AESIs)** – see Adverse Events section below.

[0379] **AESIs** – refer to Table 3 for list

Screening (within 28 days before day 1 of study)

[0380] The subject is screened to assess eligibility criteria. The following assessments and procedures are performed:

- written informed consent

- medical history, including complete history of HSV-2 infection (date of diagnosis, number of outbreaks per year, treatment, etc.), demographics, and medication and vaccine history
- complete physical examination including examination of genital area
- height and weight
- vital signs
- sample collection:
    - hematology
    - serum chemistry
    - serum pregnancy test for all women (unless surgically sterilized)
    - serum for HSV-1 and HSV-2 serology (if not previously available)
    - serum for hepatitis C virus (HCV) and HIV serology and hepatitis B surface antigen (HBsAg) testing
    - urinalysis (e.g., glucose, occult blood, protein)

Baseline Period (day -14 to day -1)

[0381] Subjects that the initial screening assessment, attend a clinic visit on the first day of the 14-day Baseline Period (Day -14). The following procedures are performed:

- Assessment of concomitant medications and vaccines
- Dispensing of valacyclovir and reminder to take valacyclovir once daily and to maintain adequate hydration and to bring all bottles to the next clinic visit
- Recording of valacyclovir dose, e.g., the previously prescribed dose (if previously taken for >6 months) or 500 mg if initiating suppressive antiviral therapy
- Provision of a pad of EQ-5D-5L questionnaires
- Instruction in use of the daily electronic reporting tool and EQ-5D-5L.

[0382] On each day during the Baseline Period, the subject:

- Records the presence or absence of genital herpes lesions, genital herpes symptoms,

and valacyclovir use via the daily electronic reporting tool

- Completes the EQ-5D-5L questionnaire
- Takes valacyclovir once a day

[0383] If Dose 1 is delayed because of active genital HSV-2 lesions or because of vaccine receipt, these procedures are continued through the delayed Dose 1 (up to an additional 3 days).

Study Vaccine (GEN-003/Placebo) Dosing Period

Day 1 (Dose 1)

[0384] The visit takes approximately 2.5 hours, including observation for 1 hour after vaccination. The following procedures are performed before IP administration:

- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Symptom-driven physical examination
- Vital signs
- Urine pregnancy test for all women (unless surgically sterilized)
- Sample collection:
  - Serum for immunogenicity testing
  - At selected investigational sites: whole blood for PBMC isolation for immunogenicity testing and human leukocyte antigen typing
- Assessment of concomitant medications and vaccines.

[0385] Any subject presenting with active genital HSV-2 lesions has Dose 1 delayed until lesions have re-epithelialized. Dose 1 may be delayed for up to 3 days; completion of the

daily electronic reporting tool and EQ-5D-5L and once daily valacyclovir is continued until delayed Dose 1.

[0386] Day 1 is delayed if a subject has received a vaccine within the excluded time frame (see Comcomitant Medications section). Dose 1 may be delayed for up to 3 days; completion of the daily electronic reporting tool and EQ-5D-5L and once daily valacyclovir is continued until delayed Dose 1.

[0387] Upon determination that a subject meets all eligibility criteria (including completion of the daily electronic reporting tool and the EQ-5D-5L and a daily valacyclovir dose on at least 11 of 14 days of the Baseline Period), the subject is randomized to treatment assignment (see, Randomization and Dosing section) and GEN-003/placebo administered.

[0388] The following procedures are performed 1 hour after GEN-003/placebo administration:

- Vital signs
- Assessment of local reactions, systemic events, and AEs

[0389] Before discharge from the clinic, the subject is given a Diary Card and instructed to record temperature, local reactions, and systemic events (at the same time each day). The subject is also instructed that, if any event is ongoing after the 7-day diary reporting period, to follow the event until resolution and report the stop date. The subject is instructed to bring the Diary Card back to the clinic at the next visit.

[0390] The subject is reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit
- Take valacyclovir once daily and maintain adequate hydration

- Bring all valacyclovir bottles to the next clinic visit.

Recurrence of Genital HSV-2

[0391] The subject returns to the investigational site within 72 hours (preferably within 24 to 48 hours) of the first time he/she notes the presence of new genital lesions after Dose 1. A clinician examines the subject to confirm the presence of genital lesions consistent with HSV-2 and, if presence confirmed, collects a lesion swab sample for detection of HSV-2 DNA.

[0392] If the subject does not attend a clinic visit or the clinician determines that the lesion observed by the subject is not consistent with genital HSV-2 or is not able to determine if the lesion is consistent with genital HSV-2 (e.g., if the lesion is no longer present), the subject is instructed to return to the clinic at the next suspected recurrence.

[0393] Completed EQ-5D-5L questionnaires are collected and a new pad is provided, if needed. Subjects are reminded to complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit.

Days 8 (+/- 3 Days) and 29 (+/- 3 Days)

[0394] The following procedures are performed:

- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Review of Diary Card
- Symptom-driven physical exam, including examination of the injection site
- Vital signs
- Sample collection:

  (a) Hematology

(b) Serum chemistry

(c) At selected investigational sites: whole blood for PBMC isolation for immunogenicity testing (Day 8 only); and

(d) Urinalysis

- Assessment of AEs
- Assessment of concomitant medications and vaccines.

[0395] The subject are reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit
- Take valacyclovir once daily and maintain adequate hydration
- Bring all valacyclovir bottles to the next clinic visit.

Doses 2 and 3 [Day 22 (+/- 3 Days) / Day 43 (+/- 3 Days)]

[0396] In no case is a dose be given within 14 days before or after another dose. The following procedures are performed before IP administration:

- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Symptom-driven physical exam
- Vital signs
- Urine pregnancy test for all women (unless surgically sterilized)

- Assessment of AEs
- Assessment of concomitant medications and vaccines.

[0397] Any subject who received a vaccine within the excluded time frame (see Concomitant Medications section) has dosing delayed until required time since vaccination has elapsed. If dosing is delayed more than 7 days after the due date, the dose is skipped.

[0398] The following procedures are performed 1 hour after GEN-003/placebo administration:

- Vital signs
- Assessment of local reactions, systemic events, and AEs.

[0399] Before discharge from the clinic, the subject is given a Diary Card and instructed to record temperature, local reactions, systemic events, and medication used for fever or pain for the first 7 days (at the same time each day). The subject is also instructed that, if any event is ongoing after the 7-day diary reporting period, to follow the event until resolution and report the stop date. The subject is instructed to bring the Diary Card back to the clinic at the next visit.

[0400] The subject is reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit
- Take valacyclovir once daily and maintain adequate hydration
- Bring all valacyclovir bottles to the next clinic visit.

[0401] At Day 43, the subject is provided with a swab kit and instructed to collect anogenital swabs for the next 28 consecutive days (prior to the Day 71/Month 1 visit).

Day 50 (+/- 3 Days) – Clinic Visit

[0402] The following procedures are performed:

- Reconciliation of number of swabs collected with the number of days collected
- Processing and storage of swabs in accordance with instructions in the Specialty Laboratory Manual
- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Review of Diary Card
- Symptom-driven physical exam, including examination of the injection site
- Vital signs
- Sample collection:
  (a) Hematology
  (b) Serum chemistry
  (c) Serum for immunogenicity testing
  (d) At selected investigational sites: whole blood for PBMC isolation for immunogenicity testing
  (e) Urinalysis
- Assessment of AEs
- Assessment of concomitant medications and vaccines.

[0403] The subject is reminded to:

- Continue use of the daily electronic reporting tool

- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit
- Take valacyclovir once daily and maintain adequate hydration
- Bring all valacyclovir bottles to the next clinic visit.

Day 71/Month 1 (+/- 3 Days) – Clinic Visit

[0404] The following procedures are performed:

- Review of swab collection procedures
- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Symptom-driven physical exam
- Vital signs
- Sample collection:
  (a) Hematology
  (b) Serum chemistry
  (c) Serum pregnancy test for all women (unless surgically sterilized)
  (d) Serum for immunogenicity testing
  (e) Urinalysis
- Assessment of AEs

- Assessment of concomitant medications and vaccines

[0405] The subject are reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit
- Take valacyclovir once daily and maintain adequate hydration; and
- Bring all valacyclovir bottles to the next clinic visit

Follow-up Period

Month 2 (Day 99 ± 7 days) / Month 3 (Day 127 +/- 7 Days) / Month 4 (Day 155 +/- 7 Days)

[0406] The following procedures are performed:

- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Assessment of SAEs and AESIs
- Assessment of antiviral and vaccine use.

[0407] The subject is reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study

- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study
- Take valacyclovir once daily and maintain adequate hydration
- Bring all valacyclovir bottles to the next clinic visit.

Month 5 (Day 183 ± 7 days)

[0408] The following procedures are performed:

- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Assessment of SAEs and AESIs
- Assessment of antiviral and vaccine use.

[0409] The subject ise provided with a swab kit and instructed to collect anogenital swabs for the next 28 consecutive days (prior to the Month 6 visit).

[0410] The subject is reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study and return the questionnaires at the next study visit
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study
- Take valacyclovir once daily and maintain adequate hydration
- Bring all valacyclovir bottles to the next clinic visit.

Month 6 (Day 211 ± 14 days)

[0411] The following procedures are performed:

- Reconciliation of number of swabs collected with the number of days collected
- Processing and storage of swabs in accordance with instructions in the Specialty Laboratory Manual
- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Symptom-driven physical examination
- Sample collection:
  - (a) Serum for immunogenicity testing
  - (b) At selected investigational sites: whole blood for PBMC isolation for immunogenicity testing
- Assessment of SAEs and AESIs
- Assessment of antiviral and vaccine use.

[0412] The subject is reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit
- Take valacyclovir once daily and maintain adequate hydration

- Bring all valacyclovir bottles to the next clinic visit.

Month 7 (Day 239 ± 14 days) / Month 8 (Day 267 ± 14 days) / Month 9 (Day 295 ± 14 days) / Month 10 (Day 323 ± 14 days)

[0413] The following procedures are performed:

- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Assessment of SAEs and AESIs
- Assessment of antiviral and vaccine use.

[0414] The subject is reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit
- Take valacyclovir once daily and maintain adequate hydration
- Bring all valacyclovir bottles to the next clinic visit

Month 11 (Day 351 ± 14 days)

[0415] The following procedures are performed:

- Return of valacyclovir bottles and dispensing of valacyclovir, if required
- Review of daily electronic reporting tool data, including review of valacyclovir dosing

- Collection of any completed EQ-5D-5L questionnaires and provision of a new pad, if needed
- Assessment of SAEs and AESIs
- Assessment of antiviral and vaccine use.

[0416] The subject is provided with a swab kit and instructed to collect anogenital swabs for the next 28 consecutive days (prior to the Month 12 visit). The subject is reminded to:

- Continue use of the daily electronic reporting tool
- Contact the investigational site to schedule a visit immediately upon suspecting the first genital herpes outbreak on study
- Complete the EQ-5D-5L questionnaire on each day genital lesions are present during the study and return the questionnaires at the next study visit
- Take valacyclovir once daily and maintain adequate hydration
- Bring all valacyclovir bottles to the next clinic visit.

Month 12 (Day 379 ± 14 days) – Clinic Visit

[0417] The following procedures are performed:

- Reconciliation of number of swabs collected with the number of days collected
- Processing and storage of swabs in accordance with instructions in the Specialty Laboratory Manual
- Return of valacyclovir bottles
- Review of daily electronic reporting tool data, including review of valacyclovir dosing
- Collection of any completed EQ-5D-5L questionnaires
- Symptom-driven physical exam
- Sample collection:

- Serum for immunogenicity testing
- At selected investigational sites: whole blood for PBMC isolation for immunogenicity testing

- Assessment of SAEs and AESIs
- Assessment of antiviral and vaccine use.

Adverse Events

[0418] AEs will be reported in a manner consistent with the FDA Guidance for Industry and Investigators, "*Safety Reporting Requirements for IND and BA/BE Studies*," December 2012 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf).

Reporting Responsibilities

[0419] All AEs (including AESIs and SAEs) will be recorded from Dose 1 to Day 71/Month 1. After Day 71/Month 1 to the end of study, only AESIs and SAEs will be recorded. It is the responsibility of the Investigator or Subinvestigator(s) to perform periodic assessment of AEs. Data describing AEs will be entered in the subject's medical record and eCRF, and as appropriate, an SAE/AESI report form. SAEs and AESIs will be reported to the Sponsor as described in below.

Definitions

[0420] **Adverse Event**: An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

[0421] **Adverse Event of Special Interest**: Table 3 for the list of AESIs.

[0422] **Serious Adverse Event**: an AE or suspected adverse reaction is considered serious (an SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- death
- life-threatening: an AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death; does not include an AE that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect.

[0423] Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. If it is not certain that an event meets the above definitions of an SAE, the Medical Monitor is contacted to discuss.

[0424] **Relatedness (Causality)**: causality (relationship to GEN-003/placebo and to valacyclovir) assessment is required for all AEs that occur during clinical studies. The following terms are used during this study:

[0425] *Likely* - reasons to consider an AE likely related to treatment may include, but are not limited, to the following:

- timing of the event relative to the administration of the IP

- location of the AE relative to the site of IP administration
- likelihood based on experience with similar products
- a biologically plausible explanation based on the mechanism of action or mode of delivery of the treatment
- the AE is repeated on subsequent treatments
- no other explanation is likely.

[0426] *Unlikely* - an AE with no temporal association with the IP but rather related to other etiologies such as concomitant medications or conditions or subject's known clinical state.

[0427] **Severity**: severity for al AEs including laboratory abnormalities is reported in accordance with Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (**Figures 1A-1D**). If an appropriate listing is not present in this table for an AE, the AE is graded as follows:

- **Grade 1 (Mild)** - no interference with daily activity
- **Grade 2 (Moderate)** - some interference with daily activity but medical intervention not required (e.g., doctor visit and/or prescription medicine); over-the-counter medicine permitted
- **Grade 3 (Severe)** - prevents daily activity and requires medical intervention (e.g., doctor visit and/or prescription medicine)
- **Grade 4 (Potentially Life-threatening)** - emergency room visit or hospitalization

Clinical Laboratory Abnormalities

[0428] Any laboratory abnormality deemed clinically significant by the Investigator is recorded as an AE. A clinically significant abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from Screening/Baseline so that in the judgment of the Investigator a change in management is warranted. This alteration includes, for example, monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

[0429] Whenever possible, the underlying medical diagnosis (e.g., anemia) is recorded as the AE term. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result are obtained when clinically indicated.

Physical Examination Abnormalities

[0430] Any physical examination abnormality deemed clinically significant by the Investigator at Screening or during the Baseline Period is reported as Medical History. Any new physical examination abnormality deemed clinically significant by the Investigator during the study is reported as an AE.

Pregnancy

[0431] The informed consent form (ICF) includes information regarding reporting of pregnancy to the Sponsor and collection of information through the end of pregnancy in both subjects and female partners of male subjects. If a female partner becomes pregnant, the Investigator requests consent from the partner to collect this information.

[0432] No additional doses of GEN-003/placebo are administered to a subject who becomes pregnant during the conduct of the trial. Subjects discuss with their health care provider the use of valacyclovir during pregnancy. All remaining safety assessments are performed. All pregnancies that occur during the study–including pregnancies in female partners of male subjects–are reported to the Sponsor on the Pregnancy eCRF and followed to conclusion. The outcome of each pregnancy is reported on the Pregnancy eCRF. Pregnancy alone is not an AE, nor is an induced elective abortion to terminate a pregnancy without medical reason. However, an induced therapeutic abortion to terminate a pregnancy due to complications or medical reasons is reported as an SAE. The underlying medical diagnosis for this procedure is reported as the SAE term. A spontaneous abortion is always considered an SAE.

Reporting of Serious Adverse Events and Adverse Events of Special Interest

[0433] SAEs and AESIs are reported to the Sponsor or designee within 1 business day of becoming aware of the event by entering the data on the AE eCRF. If at the time the Investigator submits an initial SAE/AESI report, the event has not resolved, the Investigator provides a

follow up as soon as it resolves (or upon receipt of significant information if the event is still ongoing). All SAEs/AESIs are followed until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator.

[0434] Upon checking serious or AESI on the AE eCRF, a notification is sent to the Medical Monitor and/or designee. Relevant eCRFs, including the subject's Medical History, Concomitant Medications, and other AEs are completed to provide supporting documentation for the SAE/AESI. Additional documents that support the SAE/AESI (e.g., clinic or hospital records or procedure reports), are uploaded to the AE eCRF.

[0435] After review of the initial SAE/AESI information, the Medical Monitor requests additional documentation.

[0436] The Sponsor is responsible for notifying the relevant Regulatory Authorities of certain events. It is the Investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators are notified of all unexpected, serious, IP-related events that occur during the clinical trial. Each site is responsible for notifying its IRB/EC of these additional SAEs.

Follow-Up of Adverse Events

[0437] A subject who experiences any AE, whether serious or not serious, is monitored at appropriate intervals and receives appropriate treatment and medical supervision as clinicaly indicated. All AEs are followed until resolution or stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator. Clinically significant laboratory abnormalities are confirmed within 48 hours or as soon as clinically indicated and then followed weekly until resolution.

Example 2: Sub-study of GEN-003-003 Clinical Study: Genital lesion rate in patients taking GEN-003 and an antiviral therapy

Study Design

[0438] Subjects had a documented diagnosis of genital HSV-2 infection for >1 year and a history of 3 to 9 reported clinical occurrences in the prior 12 months (or, if currently on suppressive antiviral therapy, history of at least 3 and no more than 9 reported clinical occurrences in the 12 months prior to initiation of suppressive therapy). The subjects started reporting presence or absence of genital lesions at the start of a 28-day baseline swab collection period. Following this, subjects were randomized in a 1:1:1 ratio to receive 3 IM doses of GEN-003 (described in Example 1) at a dose of 60 μg of each antigen and 50 μg of M2, or 60 μg of each antigen and 75 μg of M2, or placebo (normal saline) at intervals of 21 days (Days 1, 22, and 43).

[0439] Subjects reported to the investigational site the first time he/she noted the presence of genital lesions, and a clinician examinedthe subject to confirm the presence of genital lesions consistent with HSV-2 and, if present, collected a lesion swab sample for detection of HSV-2 DNA. Subjects reported daily the presence or absence of genitial lesions, the severity and bother of genital herpes symptoms and antiviral use via an electronic diary for the duration of the study.

[0440] The lesion rate is the proportion of days with lesions present. Lesion rates were calculated for the following periods (in addition to Baseline): Day 1 to Day 183 (6 months), and Day 1 to Day 365 (12 months) post-dosing. Antiviral use is the days of reported antiviral use in the 6-month and 12-month periods after Dose 1.

Results

[0441] The genital herpes lesion rate in subjects who received antiviral therapy in addition to GEN-003 was examined. Among subjects who took antiviral therapy, the number of days on therapy ranged widely, with some subjects only taking the antiviral medication for a few days (episodically), while others reported treating themselves chronically. Table 5 shows the antiviral therapies taken and the number of subjects.

Table 5.

Antiviral Therapies Included in this Analysis	Number of subjects
ACICLOVIR	21
FAMCICLOVIR	2
VALACICLOVIR HYDROCHLORIDE	31

[0442] A. Decreased genital lesion rate in subjects who took anti-viral therapy

[0443] The genital lesion rate of subjects in the 60 μg GEN-003 + 50 μg Matrix-M2 dose group who took any amount of antiviral during the study period was compared to the genital lesion rate of those who never took an antiviral. Figure 2 shows the change from baseline genital lesion rates separately for those who never took antiviral therapy during the study period and those who took antiviral therapy at least once. The efficacy of the vaccine formulation is improved with the addition of antiviral therapy based on a lower median change from baseline lesion rate, as shown in Table 6.

Table 6.

Antiviral Use	Median Change From Baseline Lesion Rate
No	0.0000000
Yes	-8.906074

[0444] The genital lesion rate of subjects in the 60 μg GEN-003 + 50 μg Matrix-M2 dose group was compared to the genital lesion rate of those in the placebo group. Figure 3 shows the change from baseline genital lesion rate of subjects in each of these groups who took antiviral therapy at least once during the study period. The efficacy of antiviral therapy is improved with the addition of the vaccine based on a lower median change from baseline lesion rate, as shown in Table 7.

Table 7.

Treatment Group	Median Change From Baseline Lesion Rate
GEN-003 60 µg / M2 50 µg	-8.906074
Placebo	-3.260018

[0445] B. Association between days on anti-viral therapy and decreased genital lesion rate.

[0446] The relationship between the number of days on antiviral therapy and the change from baseline genital lesion rate was also examined. Figure 4 demonstrates the association between days on anti-viral therapy and change from baseline genital lesion rate among those receiving GEN-003 60 µg / M2 50 µg. There is a downward trend in lesion rate as the number of days on antiviral therapy increases.

[0447]

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SEQUENCES

SEQ ID NO: 1 = ICP4

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EADDAAADADADEAAPASGEAVDEPAADGVVSPRQLALLASMVDEAVRTIPSPPPERDGAQEEAARSPSPPRTPSMR
ADYGEENDDDDDDDDDDDRDAGRWVRGPETTSAVRGAYPDPMASLSPRPPAPRRHHHHHHHRRRRAPRRRSAASDSS
KSGSSSSASSASSSASSSSSASASSSDDDDDDDAARAPASAADHAAGGTLGADDEEAGVPARAPGAAPRPSPPRAEP
APARTPAATAGRLERRRARAAVAGRDATGRFTAGRPRRVELDADAASGAFYARYRDGYVSGEPWPGAGPPPPGRVLY
GGLGDSRPGLWGAPEAEEARARFEASGAPAPVWAPELGDAAQQYALITRLLYTPDAEAMGWLQNPRVAPGDVALDQA
CFRISGAARNSSSFISGSVARAVPHLGYAMAAGRFGWGLAHVAAAVAMSRRYDRAQKGFLLTSLRRAYAPLLARENA
ALTGARTPDDGGDANRHDGDDARGKPAAAAAPLPSAAASPADERAVPAGYGAAGVLAALGRLSAAPASAPAGADDDD
DDDGAGGGGGGRRAEAGRVAVECLAACRGILEALAEGFDGDLAAVPGLAGARPAAPPRPGPAGAAAPPHADAPRLRA
WLRELRFVRDALVLMRLRGDLRVAGGSEAAVAAVRAVSLVAGALGPALPRSPRLLSSAAAAAADLLFQNQSLRPLLA
DTVAAADSLAAPASAPREARKRKSPAPARAPPGGAPRPPKKSRADAPRPAAAPPAGAAPPAPPTPPPRPPRPAALTR
RPAEGPDPQGGWRRQPPGPSHTPAPSAAALEAYCAPRAVAELTDHPLFPAPWRPALMFDPRALASLAARCAAPPPGG
APAAFGPLRASGPLRRAAAWMRQVPDPEDVRVVILYSPLPGEDLAAGRAGGGPPPEWSAERGGLSCLLAALGNRLCG
PATAAWAGNWTGAPDVSALGAQGVLLLSTRDLAFAGAVEFLGLLAGACDRRLIVVNAVRAADWPADGPVVSRQHAYL
ACEVLPAVQCAVRWPAARDLRRTVLASGRVFGPGVFARVEAAHARLYPDAPPLRLCRGANVRYRVRTRFGPDTLVPM
SPREYRRAVLPALDGRAAASGAGDAMAPGAPDFCEDEAHSHRACARWGLGAPLRPVYVALGRDAVRGGPAELRGPRR
EFCARALLEPDGDAPPLVLRDDADAGPPPQIRWASAAGRAGTVLAAAGGGVEVVGTAAGLATPPRREPVDMDAELED
DDDGLFGE

SEQ ID NO: 2 = ICP4 internal fragment

MVLYGGLGDSRPGLWGAPEAEEARARFEASGAPAPVWAPELGDAAQQYALITRLLYTPDAEAMGWLQNPRVAPGDVA
LDQACFRISGAARNSSSFISGSVARAVPHLGYAMAAGRFGWGLAHVAAAVAMSRRYDRAQKGFLLTSLRRAYAPLLA
RENAALTGARTPDDGGDANRRDGDDARGKPAAAAAPLPSAAASPADERAVPAGYGAAGVLAALGRLSAAPASAPAGA
DDDDDDDDGAGGGGGGGGGGGGRRAEAGRVAVECLAACRGILEALAEGFDGDLAAVPGLAGARPAAPPRPGPAGAAA
PPHADAPRLRAWLRELRFVRDALVLMRLRGDLRVAGGSEAAVAAVRAVSLVAGALGPALPRSPRLLSSAAAAAADLL
FQNQSL

SEQ ID NO: 3 = gL2

MGFVCLFGLVVMGAWGAWGGSQATEYVLRSVIAKEVGDILRVPCMRTPADDVSWRYEAPSVIDYARIDGIFLRYHCP
GLDTFLWDRHAQRAYLVNPFLFAAGFLEDLSHSVFPADTQETTTRRALYKEIRDALGSRKQAVSHAPVRAGCVNFDY
SRTRRCVGRRDLRPANTTSTWEPPVSSDDEASSQSKPLATQPPVLALSNAPPRRVSPTRGRRRHTRLRRN

SEQ ID NO: 4 = gD2 internal deletion dD2ΔTMR encoded by construct US6ΔTMR

NRWKYALADPSLKMADPNRFRGKNLPVLDQLTDPPGVKRVYHIQPSLEDPFQPPSIPITVYYAVLERACRSVLLHAP
SEAPQIVRGASDEARKHTYNLTIAWYRMGDNCAIPITVMEYTECPYNKSLGVCPIRTQPRWSYYDSFSAVSEDNLGF
LMHAPAFETAGTYLRLVKINDWTEITQFILEHRARASCKYALPLRIPPAACLTSKAYQQGVTVDSIGMLPRFIPENQ
RTVALYSLKIAGWHGPKPPYTSTLLPPELSDTTNATQPELVPEDPEDSALLEDPAGTVSSQIPPNWHIPSIQDVAPH
HAPAAPSNPRRRAQMAPKRLRLPHIRDDDAPPSHQPLFY

SEQ ID NO: 5 = predicted sequence for gD2 encoded by US6

MGRLTSGVGTAALLVVAVGLRVVCAKYALADPSLKMADPNRFRGKNLPVLDQLTDPPGVKRVYHIQPSLEDPFQPPS
IPITVYYAVLERACRSVLLHAPSEAPQIVRGASDEARKHTYNLTIAWYRMGDNCAIPITVMEYTECPYNKSLGVCPI
RTQPRWSYYDSFSAVSEDNLGFLMHAPAFETAGTYLRLVKINDWTEITQFILEHRARASCKYALPLRIPPAACLTSK
AYQQGVTVDSIGMLPRFIPENQRTVALYSLKIAGWHGPKPPYTSTLLPPELSDTTNATQPELVPEDPEDSALLEDPA
GTVSSQIPPNWHIPSIQDVAPHHAPAAPSNPGLIIGALAGSTLAVLVIGGIAFWVRRRAQMAPKRLRLPHIRDDDAP
PSHQPLFY

SEQ ID NO: 6 = ICP34.5 encoded by RL1

MSRRRGPRRRGPRRRPRPGAPAVPRPGAPAVPRPGALPTADSQMVPAYDSGTAVESAPAASSLLRRWLLVPQADDSD
DADYAGNDDAEWANSPPSEGGGKAPEAPHAAPAAACPPPPPRKERGPQRPLPPHLALRLRTTTEYLARLSLRRRRPP
ASPPADAPRGKVCFSPRVQVRHLVAWETAARLARRGSWARERADRDRFRRRVAAAEAVIGPCLEPEARARARARARA
HEDGGPAEEEEAAAAARGSSAAAGPGRRAV

SEQ ID NO: 7 = ICP0 encoded by RL2

MEPRPGTSSRADPGPERPPRQTPGTQPAAPHAWGMLNDMQWLASSDSEEETEVGISDDDLHRDSTSEAGSTDTEMFE
AGLMDAATPPARPPAERQGSPTPADAQGSCGGGPVGEEEAEAGGGGDVCAVCTDEIAPPLRCQSFPCLHPFCIPCMK
TWIPLRNTCPLCNTPVAYLIVGVTASGSFSTIPIVNDPRTRVEAEAAVRAGTAVDFIWTGNPRTAPRSLSLGGHTVR
ALSPTPPWPGTDDEDDDLADVDYVPPAPRRAPRRGGGGAGATRGTSQPAATRPAPPGAPRSSSSGGAPLRAGVGSGS
GGGPAVAAVVPRVASLPPAAGGGRAQARRVGEDAAAAEGRTPPARQPRAAQEPPIVISDSPPPSPRRPAGPGPLSFV

SSSSAQVSSGPGGGGLPQSSGRAARPRAAVAPRVRSPPRAAAAPVVSASADAAGPAPPAVPVDAHRAPRSRMTQAQT
DTQAQSLGRAGATDARGSGGPGAEGGPGVPRGTNTPGAAPHAAEGAAARPRKRRGSDSGPAASSSASSSAAPRSPLA
PQGVGAKRAAPRRAPDSDSGDRGHGPLAPASAGAAPPSASPSSQAAVAAASSSSASSSSASSSSASSSSASSSSASS
SSASSSSASSSAGGAGGSVASASGAGERRETSLGPRAAAPRGPRKCARKTRHAEGGPEPGARDPAPGLTRYLPIAGV
SSVVALAPYVNKTVTGDCLPVLDMETGHIGAYVVLVDQTGNVADLLRAAAPAWSRRTLLPEHARNCVRPPDYPTPPA
SEWNSLWMTPVGNMLFDQGTLVGALDFHGLRSRHPWSREQGAPAPAGDAPAGHGE

SEQ ID NO: 8 = ICP4 internal fragment encoded by construct RS1.1 (#1-400)

MSAEQRKKKKTTTTTQGRGAEVAMADEDGGRLRAAAETTGGPGSPDPADGPPPTPNPDRRPAARPGFGWHGGPEENE
DEADDAAADADADEAAPASGEAVDEPAADGVVSPRQLALLASMVDEAVRTIPSPPPERDGAQEEAARSPSPPRTPSM
RADYGEENDDDDDDDDDDDRDAGRWVRGPETTSAVRGAYPDPMASLSPRPPAPRRHHHHHHHRRRRAPRRRSAASDS
SKSGSSSSASSASSSASSSSSASASSSDDDDDDDAARAPASAADHAAGGTLGADDEEAGVPARAPGAAPRPSPPRAE
PAPARTPAATAGRLERRRARAAVAGRDATGRFTAGRPRRVELDADAASGAFYARYRDGYVSGEPWPGAGPPPPGRVL
YGGLGDSRPGLWGAP

SEQ ID NO: 9 = ICP4 internal fragment encoded by construct RS1.3.1 (#750-1024)

SSAAAAAADLLFQNQSLRPLLADTVAAADSLAAPASAPREARKRKSPAPARAPPGGAPRPPKKSRADAPRPAAAPPA
GAAPPAPPTPPPRPPRPAALTRRPAEGPDPQGGWRRQPPGPSHTPAPSAAALEAYCAPRAVAELTDHPLFPAPWRPA
LMFDPRALASLAARCAAPPPGGAPAAFGPLRASGPLRRAAAWMRQVPDPEDVRVVILYSPLPGEDLAAGRAGGGPPP
EWSAERGGLSCLLAALGNRLCGPATAAWAGNWTGAPDVSALGAQ

SEQ ID NO: 10 = ICP4 internal fragment encoded by construct RS1.3.2 (#1008-1319)

WAGNWTGAPDVSALGAQGVLLLSTRDLAFAGAVEFLGLLAGACDRRLIVVNAVRAADWPADGPVVSRQHAYLACEVL
PAVQCAVRWPAARDLRRTVLASGRVFGPGVFARVEAAHARLYPDAPPLRLCRGANVRYRVRTRFGPDTLVPMSPREY
RRAVLPALDGRAAASGAGDAMAPGAPDFCEDEAHSHRACARWGLGAPLRPVYVALGRDAVRGGPAELRGPRREFCAR
ALLEPDGDAPPLVLRDDADAGPPPQIRWASAAGRAGTVLAAAGGGVEVVGTAAGLATPPRREPVDMDAELEDDDDGL
FGE

SEQ ID NO: 11 = ICP4 internal fragment encoded by construct RS1.3 (#750-1319)

SSAAAAAADLLFQNQSLRPLLADTVAAADSLAAPASAPREARKRKSPAPARAPPGGAPRPPKKSRADAPRPAAAPPA
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NAVRAADWPADGPVVSRQHAYLACEVLPAVQCAVRWPAARDLRRTVLASGRVFGPGVFARVEAAHARLYPDAPPLRL
CRGANVRYRVRTRFGPDTLVPMSPREYRRAVLPALDGRAAASGAGDAMAPGAPDFCEDEAHSHRACARWGLGAPLRP
VYVALGRDAVRGGPAELRGPRREFCARALLEPDGDAPPLVLRDDADAGPPPQIRWASAAGRAGTVLAAAGGGVEVVG
TAAGLATPPRREPVDMDAELEDDDDGLFGE

SEQ ID NO: 12 = ICP4 internal fragment encoded by construct RS1.4 (#340-883)

TAGRPRRVELDADAASGAFYARYRDGYVSGEPWPGAGPPPPGRVLYGGLGDSRPGLWGAPEAEEARARFEASGAPAP
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AGRFGWGLAHVAAAVAMSRRYDRAQKGFLLTSLRRAYAPLLARENAALTGARTPDDGGDANRHDGDDARGKPAAAAA
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AYCA

SEQ ID NO: 13 = ICP4 internal fragment encoded by construct RS1.5 (#775-1318)

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EGPDPQGGWRRQPPGPSHTPAPSAAALEAYCAPRAVAELTDHPLFPAPWRPALMFDPRALASLAARCAAPPPGGAPA
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AAWAGNWTGAPDVSALGAQGVLLLSTRDLAFAGAVEFLGLLAGACDRRLIVVNAVRAADWPADGPVVSRQHAYLACE
VLPAVQCAVRWPAARDLRRTVLASGRVFGPGVFARVEAAHARLYPDAPPLRLCRGANVRYRVRTRFGPDTLVPMSPR
EYRRAVLPALDGRAAASGAGDAMAPGAPDFCEDEAHSHRACARWGLGAPLRPVYVALGRDAVRGGPAELRGPRREFC
ARALLEPDGDAPPLVLRDDADAGPPPQIRWASAAGRAGTVLAAAGGGVEVVGTAAGLATPPRREPVDMDAELEDDDD
GLFGE

SEQ ID NO: 14 = ICP4 internal fragment encoded by construct RS1.6 (#210-1318)

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VNAVRAADWPADGPVVSRQHAYLACEVLPAVQCAVRWPAARDLRRTVLASGRVFGPGVFARVEAAHARLYPDAPPLR
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SEQ ID NO: 15 = ICP4 internal fragment encoded by construct RS1.7 (deletion of #391-544)

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GPATAAWAGNWTGAPDVSALGAQGVLLLSTRDLAFAGAVEFLGLLAGACDRRLIVVNAVRAADWPADGPVVSRQHAY
LACEVLPAVQCAVRWPAARDLRRTVLASGRVFGPGVFARVEAAHARLYPDAPPLRLCRGANVRYRVRTRFGPDTLVP
MSPREYRRAVLPALDGRAAASGAGDAMAPGAPDFCEDEAHSHRACARWGLGAPLRPVYVALGRDAVRGGPAELRGPR
REFCARALLEPDGDAPPLVLRDDADAGPPPQIRWASAAGRAGTVLAAAGGGVEVVGTAAGLATPPRREPVDMDAELE
DDDDGLFGE

SEQ ID NO: 16 = ICP4 internal fragment encoded by construct RS1.8 (deletion of #786-868)

MSAEQRKKKKTTTTTQGRGAEVAMADEDGGRLRAAAETTGGPGSPDPADGPPPTPNPDRRPAARPGFGWHGGPEENE
DEADDAAADADADEAAPASGEAVDEPAADGVVSPRQLALLASMVDEAVRTIPSPPPERDGAQEEAARSPSPPRTPSM
RADYGEENDDDDDDDDDDDRDAGRWVRGPETTSAVRGAYPDPMASLSPRPPAPRRHHHHHHHRRRRAPRRRSAASDS
SKSGSSSSASSASSSASSSSSASASSSDDDDDDDAARAPASAADHAAGGTLGADDEEAGVPARAPGAAPRPSPPRAE
PAPARTPAATAGRLERRRARAAVAGRDATGRFTAGRPRRVELDADAASGAFYARYRDGYVSGEPWPGAGPPPPGRVL
YGGLGDSRPGLWGAPEAEEARARFEASGAPAPVWAPELGDAAQQYALITRLLYTPDAEAMGWLQNPRVAPGDVALDQ
ACFRISGAARNSSSFISGSVARAVPHLGYAMAAGRFGWGLAHVAAAVAMSRRYDRAQKGFLLTSLRRAYAPLLAREN
AALTGARTPDDGGDANRHDGDDARGKPAAAAAPLPSAAASPADERAVPAGYGAAGVLAALGRLSAAPASAPAGADDD
DDDDGAGGGGGGRRAEAGRVAVECLAACRGILEALAEGFDGDLAAVPGLAGARPAAPPRPGPAGAAAPPHADAPRLR
AWLRELRFVRDALVLMRLRGDLRVAGGSEAAVAAVRAVSLVAGALGPALPRSPRLLSSAAAAAADLLFQNQSLRPLL
ADTVAAADSLAAPASTPAPSAAALEAYCAPRAVAELTDHPLFPAPWRPALMFDPRALASLAARCAAPPPGGAPAAFG
PLRASGPLRRAAAWMRQVPDPEDVRVVILYSPLPGEDLAAGRAGGGPPPEWSAERGGLSCLLAALGNRLCGPATAAW
AGNWTGAPDVSALGAQGVLLLSTRDLAFAGAVEFLGLLAGACDRRLIVVNAVRAADWPADGPVVSRQHAYLACEVLP
AVQCAVRWPAARDLRRTVLASGRVFGPGVFARVEAAHARLYPDAPPLRLCRGANVRYRVRTRFGPDTLVPMSPREYR
RAVLPALDGRAAASGAGDAMAPGAPDFCEDEAHSHRACARWGLGAPLRPVYVALGRDAVRGGPAELRGPRREFCARA
LLEPDGDAPPLVLRDDADAGPPPQIRWASAAGRAGTVLAAAGGGVEVVGTAAGLATPPRREPVDMDAELEDDDDGLF
GE

SEQ ID NO: 17 = predicted sequence for uracil DNA glycosylase encoded by UL2

MFSASTTPEQPLGLSGDATPPLPTSVPLDWAAFRRAFLIDDAWRPLLEPELANPLTARLLAEYDRRCQTEEVLPPRE
DVFSWTRYCTPDDVRVVIIGQDPYHHPGQAHGLAFSVRADVPVPPSLRNVLAAVKNCYPDARMSGRGCLEKWARDGV
LLLNTTLTVKRGAAASHSKLGWDRFVGGVVQRLAARRPGLVFMLWGAHAQNAIRPDPRQHYVLKFSHPSPLSKVPFG
TCQHFLAANRYLETRDIMPIDWSV

SEQ ID NO: 18 = predicted sequence for tegument protein encoded by UL11

MGLAFSGARPCCCRHNVITTDGGEVVSLTAHEFDVVDIESEEEGNFYVPPDVRVVTRAPGPQYRRASDPPSRHTRRR
DPDVARPPATLTPPLSDSE

SEQ ID NO: 19 = gL2 secreted v.1 encoded by construct UL1s v.1

NRWGFVCLFGLVVMGAWGAWGGSQATEYVLRSVIAKEVGDILRVPCMRTPADDVSWRYEAPSVIDYARIDGIFLRYH
CPGLDTFLWDRHAQRAYLVNPFLFAAGFLEDLSHSVFPADTQETTTRRALYKEIRDALGSRKQAVSHAPVRAGCVNF
DYSRTRRCVGRRDLRPANTTSTWEPPVSSDDEASSQSKPLATQPPVLALSNAPPRRVSPTRGRRRHTRLRRN

SEQ ID NO: 20 = predicted sequence for VP5 encoded by construct UL19a

DYDIPTTENLYFQGMAAPARDPPGYRYAAAMVPTGSILSTIEVASHRRLFDFFARVRSDENSLYDVEFDALLGSYCN
TLSLVRFLELGLSVACVCTKFPELAYMNEGRVQFEVHQPLIARDGPHPVEQPVHNYMTKVIDRRALNAAFSLATEAI
ALLTGEALDGTGISLHRQLRAIQQLARNVQAVLGAFERGTADQMLHVLLEKAPPLALLLPMQRYLDNGRLATRVARA
TLVAELKRSFCDTSFFLGKAGHRREAIEAWLVDLTTATQPSVAVPRLTHADTRGRPVDGVLVTTAAIKQRLLQSFLK
VEDTEADVPVTYGEMVLNGANLVTALVMGKAVRSLDDVGRHLLEMQEEQLEANRETLDELESAPQTTRVRADLVAIG
DRLVFLEALEKRIYAATNVPYPLVGAMDLTFVLPLGLFNPAMERFAAHAGDLVPAPGHPEPRAFPPRQLFFWGKDHQ
VLRLSMENAVGTVCHPSLMNIDAAVGGVNHDPVEAANPYGAYVAAPAGPGADMQQRFLNAWRQRLAHGRVRWVAECQ
MTAEQFMQPDNANLALELHPAFDFFAGVADVELPGGEVPPAGPGAIQATWRVVNGNLPLALCPVAFRDARGLELGVG
RHAMAPATIAAVRGAFEDRSYPAVFYLLQAAIHGSEHVFCALARLVTQCITSYWNNTRCAAFVNDYSLVSYIVTYLG
GDLPEECMAVYRDLVAHVEALAQLVDDFTLPGPELGGQAQAELNHLMRDPALLPPLVWDCDGLMRHAALDRHRDCRI
DAGEHEPVYAAACNVATADFNRNDGRLLHNTQARAADAADDRPHRPADWTVHHKIYYYVLVPAFSRGRCCTAGVRFD
RVYATLQNMVVPEIAPGEECPSDPVTDPAHPLHPANLVANTVNAMFHNGRVVVDGPAMLTLQVLAHNMAERTTALLC
SAAPDAGANTASTANMRIFDGALHAGVLLMAPQHLDHTIQNGEYFYVLPVHALFAGADHVANAPNFPPALRDLARHV
PLVPPALGANYFSSIRQPVVQHARESAAGENALTYALMAGYFKMSPVALYHQLKTGLHPGFGFTVVRQDRFVTENVL
FSERASEAYFLGQLQVARHETGGGVSFTLTQPRGNVDLGVGYTAVAATATVRNPVTDMGNLPQNFYLGRGAPPLLDN
AAAVYLRNAVVAGNRLGPAQPLPVFGCAQVPRRAGMDHGQDAVCEFIATPVATDINYFRRPCNPRGRAAGGVYAGDK
EGDVIALMYDHGQSDPARPFAATANPWASQRFSYGDLLYNGAYHLNGASPVLSPCFKFFTAADITAKHRCLERLIVE
TGSAVSTATAASDVQFKRPPGCRELVEDPCGLFQEAYPITCASDPALLRSARDGEAHARETHFTQYLIYDASPLKGL
SL

SEQ ID NO: 21 = VP5 encoded by construct UL19ΔTEV

MAAPARDPPGYRYAAAMVPTGSILSTIEVASHRRLFDFFARVRSDENSLYDVEFDALLGSYCNTLSLVRFLELGLSV
ACVCTKFPELAYMNEGRVQFEVHQPLIARDGPHPVEQPVHNYMTKVIDRRALNAAFSLATEAIALLTGEALDGTGIS
LHRQLRAIQQLARNVQAVLGAFERGTADQMLHVLLEKAPPLALLLPMQRYLDNGRLATRVARATLVAELKRSFCDTS
FFLGKAGHRREAIEAWLVDLTTATQPSVAVPRLTHADTRGRPVDGVLVTTAAIKQRLLQSFLKVEDTEADVPVTYGE
MVLNGANLVTALVMGKAVRSLDDVGRHLLEMQEEQLEANRETLDELESAPQTTRVRADLVAIGDRLVFLEALEKRIY
AATNVPYPLVGAMDLTFVLPLGLFNPAMERFAAHAGDLVPAPGHPEPRAFPPRQLFFWGKDHQVLRLSMENAVGTVC
HPSLMNIDAAVGGVNHDPVEAANPYGAYVAAPAGPGADMQQRFLNAWRQRLAHGRVRWVAECQMTAEQFMQPDNANL
ALELHPAFDFFAGVADVELPGGEVPPAGPGAIQATWRVVNGNLPLALCPVAFRDARGLELGVGRHAMAPATIAAVRG

AFEDRSYPAVFYLLQAAIHGSEHVFCALARLVTQCITSYWNNTRCAAFVNDYSLVSYIVTYLGGDLPEECMAVYRDL
VAHVEALAQLVDDFTLPGPELGGQAQAELNHLMRDPALLPPLVWDCDGLMRHAALDRHRDCRIDAGEHEPVYAAACN
VATADFNRNDGRLLHNTQARAADAADDRPHRPADWTVHHKIYYYVLVPAFSRGRCCTAGVRFDRVYATLQNMVVPEI
APGEECPSDPVTDPAHPLHPANLVANTVNAMFHNGRVVVDGPAMLTLQVLAHNMAERTTALLCSAAPDAGANTASTA
NMRIFDGALHAGVLLMAPQHLDHTIQNGEYFYVLPVHALFAGADHVANAPNFPPALRDLARHVPLVPPALGANYFSS
IRQPVVQHARESAAGENALTYALMAGYFKMSPVALYHQLKTGLHPGFGFTVVRQDRFVTENVLFSERASEAYFLGQL
QVARHETGGGVSFTLTQPRGNVDLGVGYTAVAATATVRNPVTDMGNLPQNFYLGRGAPPLLDNAAAVYLRNAVVAGN
RLGPAQPLPVFGCAQVPRRAGMDHGQDAVCEFIATPVATDINYFRRPCNPRGRAAGGVYAGDKEGDVIALMYDHGQS
DPARPFAATANPWASQRFSYGDLLYNGAYHLNGASPVLSPCFKFFTAADITAKHRCLERLIVETGSAVSTATAASDV
QFKRPPGCRELVEDPCGLFQEAYPITCASDPALLRSARDGEAHARETHFTQYLIYDASPLKGLSL

SEQ ID NO: 22 = predicted sequence for ICP1/2 encoded by UL36

MIPAALPHPTMKRQGDRDIVVTGVRNQFATDLEPGGSVSCMRSSLSFLSLLFDVGPRDVLSAEAIEGCLVEGGEWTR
AAAGSGPPRMCSIIELPNFLEYPAARGGLRCVFSRVYGEVGFFGEPTAGLLETQCPAHTFFAGPWAMRPLSYTLLTI
GPLGMGLYRDGDTAYLFDPHGLPAGTPAFIAKVRAGDVYPYLTYYAHDRPKVRWAGAMVFFVPSGPGAVAPADLTAA
ALHLYGASETYLQDEPFVERRVAITHPLRGEIGGLGALFVGVVPRGDGEGSGPVVPALPAPTHVQTPGADRPPEAPR
GASGPPDTPQAGHPNRPPDDVWAAALEGTPPAKPSAPDAAASGPPHAAPPPQTPAGDAAEEAEDLRVLEVGAVPVGR
HRARYSTGLPKRRRPTWTPPSSVEDLTSGERPAPKAPPAKAKKKSAPKKKAPVAAEVPASSPTPIAATVPPAPDTPP
QSGQGGGDDGPASPSSPSVLETLGARRPPEPPGADLAQLFEVHPNVAATAVRLAARDAALAREVAACSQLTINALRS
PYPAHPGLLELCVIFFFERVLAFLIENGARTHTQAGVAGPAAALLDFTLRMLPRKTAVGDFLASTRMSLADVAAHRP
LIQHVLDENSQIGRLALAKLVLVARDVIRETDAFYGDLADLDLQLRAAPPANLYARLGEWLLERSRAHPNTLFAPAT
PTHPEPLLHRIQALAQFARGEEMRVEAEAREMREALDALARGVDSVSQRAGPLTVMPVPAAPGAGGRAPCPPALGPE
AIQARLEDVRIQARRAIESAVKEYFHRGAVYSAKALQASDSHDCRFHVASAAVVPMVQLLESLPAFDQHTRDVAQRA
ALPPPPPLATSPQAILLRDLLQRGQPLDAPEDLAAWLSVLTDAATQGLIERKPLEELARSIHGINDQQARRSSGLAE
LQRFDALDAALAQQLDSDAAFVPATGPAPYVDGGGLSPEATRMAEDALRQARAMEAAKMTAELAPEARSRLRERAHA
LEAMLNDARERAKVAHDAREKFLHKLQGVLRPLPDFVGLKACPAVLATLRASLPAGWTDLADAVRGPPPEVTAALRA
DLWGLLGQYREALEHPTPDTATALAGLHPAFVVVLKTLFADAPETPVLVQFFSDHAPTIAKAVSNAINAGSAAVATA
SPAATVDAAVRAHGALADAVSALGAAARDPASPLSFLAVLADSAAGYVKATRLALEARGAIDELTTLGSAAADLVVQ
ARRACAQPEGDHAALIDAAARATTAARESLAGHEAGFGGLLHAEGTAGDHSPSGRALQELGKVIGATRRRADELEAA
VADLTAKMAAQRARGSSERWAAGVEAALDRVENRAEFDVVELRRLQALAGTHGYNPRDFRKRAEQALAANAEAVTLA
LDTAFAFNPYTPENQRHPMLPPLAAIHRLGWSAAFHAAAETYADMFRVDAEPLARLLRIAEGLLEMAQAGDGFIDYH
EAVGRLADDMTSVPGLRRYVPFFQHGYADYVELRDRLDAIRADVHRALGGVPLDLAAAAEQISAARNDPEATAELVR
TGVTLPCPSEDALVACAAALERVDQSPVKNTAYAEYVAFVTRQDTAETKDAVVRAKQQRAEATERVMAGLREALAAR
ERRAQIEAEGLANLKTMLKVVAVPATVAKTLDQARSVAEIADQVEVLLDQTEKTRELDVPAVIWLEHAQRTFETHPL
SAARGDGPGPLARHAGRLGALFDTRRRVDALRRSLEEAEAEWDEVWGRFGRVRGGAWKSPEGFRAMHEQLRALQDTT

NTVSGLRAQPAYERLSARYQGVLGAKGAERAEAVEELGARVTKHTALCARLRDEVVRRVPWEMNFDALGGLLAEFDA
AAADLAPWAVEEFRGARELIQYRMGLYSAYARAGGQTGAGAESAPAPLLVDLRALDARARASSSPEGHEVDPQLLRR
RGEAYLRAGGDPGPLVLREAVSALDLPFATSFLAPDGTPLQYALCFPAVTDKLGALLMRPEAACVRPPLPTDVLESA
PTVTAMYVLTVVNRLQLALSDAQAANFQLFGRFVRHRQATWGASMDAAAELYVALVATTLTREFGCRWAQLGWASGA
AAPRPPPGPRGSQRHCVAFNENDVLVALVAGVPEHIYNFWRLDLVRQHEYMHLTLERAFEDAAESMLFVQRLTPHPD
ARIRVLPTFLDGGPPTRGLLFGTRLADWRRGKLSETDPLAPWRSALELGTQRRDVPALGKLSPAQALAAVSVLGRMC
LPSAALAALWTCMFPDDYTEYDSFDALLAARLESGQTLGPAGGREASLPEAPHALYRPTGQHVAVLAAATHRTPAAR
VTAMDLVLAAVLLGAPVVVALRNTTAFSRESELELCLTLFDSRPGGPDAALRDVVSSDIETWAVGLLHTDLNPIENA
CLAAQLPRLSALIAERPLADGPPCLVLVDISMTPVAVLWEAPEPPGPPDVRFVGSEATEELPFVATAGDVLAASAAD
ADPFFARAILGRPFDASLLTGELFPGHPVYQRPLADEAGPSAPTAARDPRDLAGGDGGSGPEDPAAPPARQADPGVL
APTLLTDATTGEPVPPRMWAWIHGLEELASDDAGGPTPNPAPALLPPPATDQSVPTSQYAPRPIGPAATARETRPSV
PPQQNTGRVPVAPRDDPRPSPPTPSPPADAALPPPAFSGSAAAFSAAVPRVRRSRRTRAKSRAPRASAPPEGWRPPA
LPAPVAPVAASARPPDQPPTPESAPPAWVSALPLPPGPASARGAFPAPTLAPIPPPPAEGAVVPGGDRRRGRRQTTA
GPSPTPPRGPAAGPPRRLTRPAVASLSASLNSLPSPRDPADHAAAVSAAAAAVPPSPGLAPPTSAVQTSPPPLAPGP
VAPSEPLCGWVVPGGPVARRPPPQSPATKPAARTRIRARSVPQPPLPQPPLPQPPLPQPPLPQPPLPQPPLPQPPLP
QPPLPQPPLPQPPLPQPPLPPVTRTLTPQSRDSVPTPESPTHTNTHLPVSAVTSWASSLALHVDSAPPPASLLQTLH
ISSDDEHSDADSLRFSDSDDTEALDPLPPEPHLPPADEPPGPLAADHLQSPHSQFGPLPVQANAVLSRRYVRSTGRS
ALAVLIRACRRIQQQLQRTRRALFQRSNAVLTSLHHVRMLLG

SEQ ID NO: 23 = ICP1/2 internal fragment encoded by construct UL36.3.4.1

AAQRARGSSERWAAGVEAALDRVENRAEFDVVELRRLQALAGTHGYNPRDFRKRAEQALAANAEAVTLALDTAFAFN
PYTPENQRHPMLPPLAAIHRLGWSAAFHAAAETYADMFRVDAEPLARLLRIAEGLLEMAQAGDGFIDYHEAVGRLAD
DMTSVPGLRRYVPFFQHGYADYVELRDRLDAIRADVHRALGGVPLDLAAAAEQISAARNDPEATAELVRTGVTLPCP
SEDALVACAAALERVDQSPVKNTAYAEYVAFVTRQDTAETKDAVVRAKQQRAEATERVMAGLREALAARERRAQIEA
EGLANLKTMLKVVAVPATVAKTLDQARSVAEIADQVEVLLDQTEKTRELDVPAVIWLEHAQRTFETHPLSAARGDGP
GPLARHAGRLGALFDTRRRVDALRRSLEEAEAEWDEVWGRFGRVRGGAWKSPEGFRAMHEQLRALQDTTNTVSGLRA
QPAYERLSARYQGVLGAKGAERAEAVEELGARVTKHTALCARLRDEVVRRVPWEMNFDALGGLLAEFDAAAADLAPW
AVEEFRGARELIQYRMGLYSAYARAGGQTGAGAESAPAPLLVDLRALDARARASSSPEGHEVDPQLLRRRGEAYLRA
GGDPGPLVLREAVSALDLPFATSFLAPDGTPLQYALCFPAVTDKLGALLMRPEAACVRPPLPTDVLESAPTVTAMYV
LTVVNRLQLALSDAQAANFQLFGRFVRHRQATWGASMDAAAELYVALVATTLTREFGCRWAQLGWASGAAAPRPPPG
PRGSQRHCVAFNENDVLVALVAGVPEHIYNFWRLDLVRQHEYMHLTLERAFEDAAESMLFVQRLTPHPDARIRVLPT
FLDGGPPTRGLLFGTRLADWRRGKLSETDPLAPWRSALELGTQRRDVPALGKLSPAQALAAVSVLGRMCLPSAALAA
LWTCMFPDDYTEYDSFDALLAARLESGQTLGPAGGREASL

SEQ ID NO: 24 = ICP1/2 internal fragment encoded by construct UL36.4.2.5

EYDSFDALLAARLESGQTLGPAGGREASLPEAPHALYRPTGQHVAVLAAATHRTPAARVTAMDLVLAAVLLGAPVVV
ALRNTTAFSRESELELCLTLFDSRPGGPDAALRDVVSSDIETWAVGLLHTDLNPIENACLAAQLPRLSALIAERPLA
DGPPCLVLVDISMTPVAVLWEAPEPPGPPDVRFVGSEATEELPFVATAGDVLAASAADADPFFARAILGRPFDASLL
TGELFPGHPVYQRPLADEAGPSAPTAARDPRDLAGGDGGSGPEDPAAPPARQADPGVLAPTLLTDATTGEPVPPRMW
AWIHGLEELASDDAGGPTPNPAPALLPPPATDQSVPTSQYAPRPIGPAATARETRPSVPPQQNTGRVPVAPRDDPRP
SPPTPSPPADAALPPPAFSGSAAAFSAAVPRVRRSRRTRAKSRAPRASAPPEGWRPPALPAPVAPVAASARPPDQPP
TPESAPPAWVSALPLPPGPASARGAFPAPTLAPIPPPPAEGAVVPGGDRRRGRRQTTAGPSPTPPRGPAAGPPRRLT
RPAVASLSASLNSLPSPRDPADHAAAVSAAAAAVPPSPGLAPPTSAVQTSPPPLAPGPVAPSEPLCGWVVPGGPVAR
RPPPQSPATKPAARTRIRARSVPQPPLPQPPLPQPPLPQPPLPQPPLPQPPLPQPPLPQPPLPQPPLPQPPLPQPPL
PPVTRTLTPQSRDSVPTPESPTHTNTHLPVSAVTSWASSLALHVDSAPPPASLLQTLHISSDDEHSDADSLRFSDSD
DTEALDPLPPEPHLPPADEPPGPLAADHLQSPHSQFGPLPVQANAVLSRRYVRSTGRSALAVLIRACRRIQQQLQRT
RRALFQRSNAVLTSLHHVRMLLG

SEQ ID NO: 25 = predicted sequence for reductase encoded by UL40

MDPAVSPASTDPLDTHASGAGAAPIPVCPTPERYFYTSQCPDINHLRSLSILNRWLETELVFVGDEEDVSKLSEGEL
GFYRFLFAFLSAADDLVTENLGGLSGLFEQKDILHYYVEQECIEVVHSRVYNIIQLVLFHNNDQARRAYVARTINHP
AIRVKVDWLEARVRECDSIPEKFILMILIEGVFFAASFAAIAYLRTNNLLRVTCQSNDLISRDEAVHTTASCYIYNN
YLGGHAKPEAARVYRLFREAVDIEIGFIRSQAPTDSSILSPGALAAIENYVRFSADRLLGLIHMQPLYSAPAPDASF
PLSLMSTDKHTNFFECRSTSYAGAVVNDL

SEQ ID NO: 26 = ICP47 encoded by US12

MSWALKTTDMFLDSSRCTHRTYGDVCAEIHKREREDREAARTAVTDPELPLLCPPDVRSDPASRNPTQQTRGCARSN
ERQDRVLAP

SEQ ID NO: 27 = gM2 encoded by UL10

MGRRAPRGSPEAAPGADVAPGARAAWWVWCVQVATFIVSAICVVGLLVLASVFRDRFPCLYAPATSYAKANATVEVR
GGVAVPLRLDTQSLLATYAITSTLLLAAAVYAAVGAVTSRYERALDAARRLAAARMAMPHATLIAGNVCAWLLQITV
LLLAHRISQLAHLIYVLHFACLVYLAAHFCTRGVLSGTYLRQVHGLIDPAPTHHRIVGPVRAVMTNALLLGTLLCTA
AAAVSLNTIAALNFNFSAPSMLICLTTLFALLVVSLLLVVEGVLCHYVRVLVGPHLGAIAATGIVGLACEHYHTGGY
YVVEQQWPGAQTGVRVALALVAAFALAMAVLRCTRAYLYHRRHHTKFFVRMRDTRHRAHSALRRVRSSMRGSRRGGP

PGDPGYAETPYASVSHHAEIDRYGDSDGDPIYDEVAPDHEAELYARVQRPGPVPDAEPIYDTVEGYAPRSAGEPVYS
TVRRW

SEQ ID NO: 28 = predicted sequence for cleavage/packaging protein encoded by UL15

MFGQQLASDVQQYLERLEKQRQQKVGVDEASAGLTLGGDALRVPFLDFATATPKRHQTVVPGVGTLHDCCEHSPLFS
AVARRLLFNSLVPAQLRGRDFGGDHTAKLEFLAPELVRAVARLRFRECAPEDAVPQRNAYYSVLNTFQALHRSEAFR
QLVHFVRDFAQLLKTSFRASSLAETTGPPKKRAKVDVATHGQTYGTLELFQKMILMHATYFLAAVLLGDHAEQVNTF
LRLVFEIPLFSDTAVRHFRQRATVFLVPRRHGKTWFLVPLIALSLASFRGIKIGYTAHIRKATEPVFDEIDACLRGW
FGSSRVDHVKGETISFSFPDGSRSTIVFASSHNTNGIRGQDFNLLFVDEANFIRPDAVQTIMGFLNQANCKIIFVSS
TNTGKASTSFLYNLRGAADELLNVVTYICDDHMPRVVTHTNATACSCYILNKPVFITMDGAVRRTADLFLPDSFMQE
IIGGQARETGDDRPVLTKSAGERFLLYRPSTTTNSGLMAPELYVYVDPAFTANTRASGTGIAVVGRYRDDFIIFALE
HFFLRALTGSAPADIARCVVHSLAQVLALHPGAFRSVRVAVEGNSSQDSAVAIATHVHTEMHRILASAGANGPGPEL
LFYHCEPPGGAVLYPFFLLNKQKTPAFEYFIKKFNSGGVMASQELVSVTVRLQTDPVEYLSEQLNNLIETVSPNTDV
RMYSGKRNGAADDLMVAVIMAIYLAAPTGIPPAFFPITRTS

SEQ ID NO: 29 = predicted sequence for ICP35 encoded by UL26.5

MNPVSASGAPAPPPPGDGSYLWIPASHYNQLVTGQSAPRHPPLTACGLPAAGTVAYGHPGAGPSPHYPPPPAHPYPG
MLFAGPSPLEAQIAALVGAIAADRQAGGLPAAAGDHGIRGSAKRRRHEVEQPEYDCGRDEPDRDFPYYPGEARPEPR
PVDSRRAARQASGPHETITALVGAVTSLQQELAHMRARTHAPYGPYPPVGPYHHPHADTETPAQPPRYPAKAVYLPP
PHIAPPGPPLSGAVPPPSYPPVAVTPGPAPPLHQPSPAHAHPPPPPPGPTPPPAASLPQPEAPGAEAGALVNASSAA
HVNVDTARAADLFVSQMMGSR

SEQ ID NO: 30 = predicted sequence for polymerase encoded by UL30

MFCAAGGPASPGGKPAARAASGFFAPHNPRGATQTAPPPCRRQNFYNPHLAQTGTQPKALGPAQRHTYYSECDEFRF
IAPRSLDEDAPAEQRTGVHDGRLRRAPKVYCGGDERDVLRVGPEGFWPRRLRLWGGADHAPEGFDPTVTVFHVYDIL
EHVEHAYSMRAAQLHERFMDAITPAGTVITLLGLTPEGHRVAVHVYGTRQYFYMNKAEVDRHLQCRAPRDLCERLAA
ALRESPGASFRGISADHFEAEVVERADVYYYETRPTLYYRVFVRSGRALAYLCDNFCPAIRKYEGGVDATTRFILDN
PGFVTFGWYRLKPGRGNAPAQPRPPTAFGTSSDVEFNCTADNLAVEGAMCDLPAYKLMCFDIECKAGGEDELAFPVA
ERPEDLVIQISCLLYDLSTTALEHILLFSLGSCDLPESHLSDLASRGLPAPVVLEFDSEFEMLLAFMTFVKQYGPEF
VTGYNIINFDWPFVLTKLTEIYKVPLDGYGRMNGRGVFRVWDIGQSHFQKRSKIKVNGMVNIDMYGIITDKVKLSSY
KLNAVAEAVLKDKKKDLSYRDIPAYYASGPAQRGVIGEYCVQDSLLVGQLFFKFLPHLELSAVARLAGINITRTIYD
GQQIRVFTCLLRLAGQKGFILPDTQGRFRGLDKEAPKRPAVPRGEGERPGDGNGDEDKDDDEDGDEDGDEREEVARE

TGGRHVGYQGARVLDPTSGFHVDPVVVFDFASLYPSIIQAHNLCFSTLSLRPEAVAHLEADRDYLEIEVGGRRLFFV
KAHVRESLLSILLRDWLAMRKQIRSRIPQSTPEEAVLLDKQQAAIKVVCNSVYGFTGVQHGLLPCLHVAATVTTIGR
EMLLATRAYVHARWAEFDQLLADFPEAAGMRAPGPYSMRIIYGDTDSIFVLCRGLTAAGLVAMGDKMASHISRALFL
PPIKLECEKTFTKLLLIAKKKYIGVICGGKMLIKGVDLVRKNNCAFINRTSRALVDLLFYDDTVSGAAAALAERPAE
EWLARPLPEGLQAFGAVLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLAHLTVYYKLMARRAQVPSIKDRIP
YVIVAQTREVEETVARLAALRELDAAAPGDEPAPPAALPSPAKRPRETPSHADPPGGASKPRKLLVSELAEDPGYAI
ARGVPLNTDYYFSHLLGAACVTFKALFGNNAKITESLLKRFIPETWHPPDDVAARLRAAGFGPAGAGATAEETRRML
HRAFDTLA

SEQ ID NO: 31 = predicted sequence for helicase/primase complex encoded by UL5

MAASGGEGSRDVRAPGPPPQQPGARPAVRFRDEAFLNFTSMHGVQPIIARIRELSQQQLDVTQVPRLQWFRDVAALE
VPTGLPLREFPFAAYLITGNAGSGKSTCVQTLNEVLDCVVTGATRIAAQNMYVKLSGAFLSRPINTIFHEFGFRGNH
VQAQLGQHPYTLASSPASLEDLQRRDLTYYWEVILDITKRALAAHGGEDARNEFHALTALEQTLGLGQGALTRLASV
THGALPAFTRSNIIVIDEAGLLGRHLLTTVVYCWWMINALYHTPQYAGRLRPVLVCVGSPTQTASLESTFEHQKLRC
SVRQSENVLTYLICNRTLREYTRLSHSWAIFINNKRCVEHEFGNLMKVLEYGLPITEEHMQFVDRFVVPESYITNPA
NLPGWTRLFSSHKEVSAYMAKLHAYLKVTREGEFVVFTLPVLTFVSVKEFDEYRRLTQQPTLTMEKWITANASRITN
YSQSQDQDAGHVRCEVHSKQQLVVARNDITYVLNSQVAVTARLRKMVFGFDGTFRTFEAVLRDDSFVKTQGETSVEF
AYRFLSRLMFGGLIHFYNFLQRPGLDATQRTLAYGRLGELTAELLSLRRDAAGASATRAADTSDRSPGERAFNFKHL
GPRDGGPDDFPDDDLDVIFAGLDEQQLDVFYCHYALEEPETTAAVHAQFGLLKRAFLGRYLILRELFGEVFESAPFS
TYVDNVIFRGCELLTGSPRGGLMSVALQTDNYTLMGYTYTRVFAFAEELRRRHATAGVAEFLEESPLPYIVLRDQHG
FMSVVNTNISEFVESIDSTELAMAINADYGISSKLAMTITRSQGLSLDKVAICFTPGNLRLNSAYVAMSRTTSSEFL
HMNLNPLRERHERDDVISEHILSALRDPNVVIVY

SEQ ID NO: 32 = predicted sequence for helicase/primase complex encoded by UL8

MEAPGIVWVEESVSAITLYAVWLPPRTRDCLHALLYLVCRDAAGEARARFAEVSVGSSDLQDFYGSPDVSAPGAVAA
ARAATAPAASPLEPLGDPTLWRALYACVLAALERQTGRWALFVPLRLGWDPQTGLVVRVERASWGPPAAPRAALLDV
EAKVDVDPLALSARVAEHPGARLAWARLAAIRDSPQCASSASLAVTITTRTARFAREYTTLAFPPTRKEGAFADLVE
VCEVGLRPRGHPQRVTARVLLPRGYDYFVSAGDGFSAPALVALFRQWHTTVHAAPGALAPVFAFLGPGFEVRGGPVQ
YFAVLGFPGWPTFTVPAAAAAESARDLVRGAAATHAACLGAWPAVGARVVLPPRAWPAVASEAAGRLLPAFREAVAR
WHPTATTIQLLDPPAAVGPVWTARFCFSGLQAQLLAALAGLGEAGLPEARGRAGLERLDALVAAAPSEPWARAVLER
LVPDACDACPALRQLLGGVMAAVCLQIEQTASSVKFAVCGGTGAAFWGLFNVDPGDADAAHGAIQDARRALEASVRA
VLSANGIRPRLAPSLAPEGVYTHVVTWSQTGAWFWNSRDDTDFLQGFPLRGAAYAAAAEVMRDALRRILRRPAAGPP

EEAVCAARGVMEDACDRFVLDAFGRRLDAEYWSVLTPPGEADDPLPQTAFRGGALLDAEQYWRRVVRVCPGGGESVG
VPVDLYPRPLVLPPVDCAHHLREILREIQLVFTGVLEGVWGEGGSFVYPFDEKIRFLFP

SEQ ID NO: 33 = predicted sequence for unknown protein encoded by UL15.5

MDGAVRRTADLFLPDSFMQEIIGGQARETGDDRPVLTKSAGERFLLYRPSTTTNSGLMAPELYVYVDPAFTANTRAS
GTGIAVVGRYRDDFIIFALEHFFLRALTGSAPADIARCVVHSLAQVLALHPGAFRSVRVAVEGNSSQDSAVAIATHV
HTEMHRILASAGANGPGPELLFYHCEPPGGAVLYPFFLLNKQKTPAFEYFIKKFNSGGVMASQELVSVTVRLQTDPV
EYLSEQLNNLIETVSPNTDVRMYSGKRNGAADDLMVAVIMAIYLAAPTGIPPAFFPITRTS

SEQ ID NO: 34 = predicted sequence for packaging protein encoded by UL32

MATSAPGVPSSAAVREESPGSSWKEGAFERPYVAFDPDLLALNEALCAELLAACHVVGVPPASALDEDVESDVAPAP
PRPRGAAREASGGRGPGSARGPPADPTAEGLLDTGPFAAASVDTFALDRPCLVCRTIELYKQAYRLSPQWVADYAFL
CAKCLGAPHCAASIFVAAFEFVYVMDHHFLRTKKATLVGSFARFALTINDIHRHFFLHCCFRTDGGVPGRHAQKQPR
PTPSPGAAKVQYSNYSFLAQSATRALIGTLASGGDDGAGAGAGGGSGTQPSLTTALMNWKDCARLLDCTEGKRGGGD
SCCTRAAARNGEFEAAAGALAQGGEPETWAYADLILLLLAGTPAVWESGPRLRAAADARRAAVSESWEAHRGARMRD
AAPRFAQFAEPQPQPDLDLGPLMATVLKHGRGRGRTGGECLLCNLLLVRAYWLAMRRLRASVVRYSENNTSLFDCIV
PVVDQLEADPEAQPGDGGRFVSLLRAAGPEAIFKHMFCDPMCAITEMEVDPWVLFGHPRADHRDELQLHKAKLACGN
EFEGRVCIALRALIYTFKTYQVFVPKPTALATFVREAGALLRRHSISLLSLEHTLCTYV

SEQ ID NO: 35 = predicted sequence for ICP1/2 fragment encoded by construct UL36.4.2

MEYDSFDALLAARLESGQTLGPAGGREASLPEAPHALYRPTGQHVAVLAAATHRTPAARVTAMDLVLAAVLLGAPVV
VALRNTTAFSRESELELCLTLFDSRPGGPDAALRDVVSSDIETWAVGLLHTDLNPIENACLAAQLPRLSALIAERPL
ADGPPCLVLVDISMTPVAVLWEAPEPPGPPDVRFVGSEATEELPFVATAGDVLAASAADADPFFARAILGRPFDASL
LTGELFPGHPVYQRPLADEAGPSAPTAARDPRDLAGGDGGSGPEDPAAPPARQADPGVLAPTLLTDATTGEPVPPRM
WAWIHGLEELASDDAGGPT

SEQ ID NO: 36 = predicted sequence for ICP27 encoded by UL54

MATDIDMLIDLGLDLSDSELEEDALERDEEGRRDDPESDSSGECSSSDEDMEDPCGDGGAEAIDAAIPKGPPARPED
AGTPEASTPRPAARRGADDPPPATTGVWSRLGTRRSASPREPHGGKVARIQPPSTKAPHPRGGRRGRRRGRGRYGPG
GADSTPKPRRRVSRNAHNQGGRHPASARTDGPGATHGEARRGGEQLDVSGGPRPRGTRQAPPPLMALSLTPPHADGR
APVPERKAPSADTIDPAVRAVLRSISERAAVERISESFGRSALVMQDPFGGMPFPAANSPWAPVLATQAGGFDAETR

RVSWETLVAHGPSLYRTFAANPRAASTAKAMRDCVLRQENLIEALASADETLAWCKMCIHHNLPLRPQDPIIGTAAA
VLENLATRLRPFLQCYLKARGLCGLDDLCSRRRLSDIKDIASFVLVILARLANRVERGVSEIDYTTVGVGAGETMHF
YIPGACMAGLIEILDTHRQECSSRVCELTASHTIAPLYVHGKYFYCNSLF

SEQ ID NO: 37 = virion protein encoded by UL49.5

MTGKPARLGRWVVLLFVALVAGVPGEPPNAAGARGVIGDAQCRGDSAGVVSVPGVLVPFYLGMTSMGVCMIAHVYQI
CQRALAAGSA

SEQ ID NO: 38 = gG2 encoded by US4

NRWGSGVPGPINPPNSDVVFPGGSPVAQYCYAYPRLDDPGPLGSADAGRQDLPRRVVRHEPLGRSFLTGGLVLLAPP
VRGFGAPNATYAARVTYYRLTRACRQPILLRQYGGCRGGEPPSPKTCGSYTYTYQGGGPPTRYALVNASLLVPIWDR
AAETFEYQIELGGELHVGLLWVEVGGEGPGPTAPPQAARAEGGPCVPPVPAGRPWRSVPPVWYSAPNPGFRGLRFRE
RCLPPQTPAAPSDLPRVAFAPQSLLVGITGRTFIRMARPTEDVGVLPPHWAPGALDDGPYAPFPPRPRFRR

SEQ ID NO: 39 = RS1

ATGTCGTACTACCATCACCATCACCATCACAGTGCCGAACAGCGTAAAAAGAAAAAAACCACCACCACGACCCAAGG
ACGTGGAGCTGAAGTTGCTATGGCGGATGAGGATGGAGGCCGCTTGAGAGCTGCTGCTGAGACTACTGGAGGACCTG
GATCACCGGACCCTGCCGATGGACCCCCCCCTACACCAAACCCCGATCGTAGACCGGCTGCTAGACCTGGATTCGGA
TGGCATGGAGGACCCGAGGAAAACGAGGACGAGGCGGACGACGCCGCTGCCGACGCCGACGCCGATGAGGCTGCCCC
TGCTTCTGGAGAGGCGGTAGACGAACCTGCTGCCGATGGAGTTGTTAGCCCTAGGCAATTGGCTTTGTTGGCGAGCA
TGGTAGACGAGGCTGTGAGAACAATCCCTTCCCCTCCCCCTGAACGTGATGGAGCACAAGAGGAGGCGGCTAGGAGT
CCCTCACCACCCCGTACACCTTCTATGAGAGCGGATTACGGCGAGGAAAACGACGACGACGACGATGATGATGACGA
CGATGATCGTGATGCCGGACGCTGGGTTAGGGGACCTGAAACCACTTCTGCTGTCCGTGGAGCATACCCCGATCCTA
TGGCGAGTTTGAGCCCTAGACCACCTGCCCCGAGGAGACACCACCACCACCACCATCATAGGCGTAGACGTGCTCCT
AGACGTCGTTCTGCCGCTAGTGACTCTTCCAAATCTGGCTCTTCTTCATCTGCCTCTTCCGCTTCATCTTCGGCCTC
ATCGTCCTCTTCGGCATCCGCTTCGAGTAGTGATGATGATGATGACGACGACGCTGCTAGAGCCCCCGCTTCTGCTG
CCGACCACGCTGCTGGCGGAACTTTGGGAGCCGACGACGAGGAGGCGGGAGTTCCTGCTCGTGCCCCGGGAGCTGCT
CCGAGGCCTTCTCCACCCCGTGCTGAACCTGCTCCGGCTAGAACACCGGCCGCTACTGCTGGTAGACTGGAGCGTAG
ACGTGCCCGTGCTGCTGTGGCTGGTAGAGATGCTACTGGCCGCTTCACTGCTGGCCGTCCTAGACGTGTTGAACTGG
ACGCCGATGCTGCTTCTGGTGCTTTCTACGCCCGTTACCGTGATGGTTACGTGTCTGGTGAACCTTGGCCTGGCGCT
GGTCCACCTCCGCCCGGACGTGTACTCTACGGTGGATTGGGCGATTCTCGCCCTGGTCTGTGGGGCGCTCCGGAGGC
TGAGGAGGCTAGAGCCCGTTTCGAGGCTTCTGGTGCCCCTGCTCCTGTTTGGGCTCCTGAATTGGGCGACGCTGCTC

AACAATACGCCCTCATCACACGCTTGCTGTACACTCCCGACGCCGAGGCTATGGGATGGCTCCAAAACCCTAGAGTT
GCCCCTGGTGATGTTGCTCTGGATCAGGCTTGTTTCCGTATCTCCGGCGCTGCTCGTAACTCTTCTTCGTTCATCTC
CGGTTCTGTGGCTAGAGCTGTGCCTCACTTGGGATACGCCATGGCCGCTGGACGTTTCGGCTGGGGACTGGCTCATG
TTGCTGCCGCTGTAGCAATGTCTAGACGCTACGACCGTGCTCAAAAAGGATTCTTGCTCACGTCACTGAGGCGTGCT
TACGCCCCTTTGTTGGCCCGTGAAAACGCTGCCCTCACTGGCGCCCGTACCCCCGATGACGGTGGCGACGCCAACCG
CCACGATGGTGATGATGCTAGAGGCAAACCCGCTGCCGCTGCTGCTCCTTTGCCCTCTGCCGCCGCTTCCCCTGCCG
ATGAACGTGCTGTTCCTGCCGGTTACGGTGCCGCTGGTGTGTTGGCTGCTTTGGGACGCTTGAGTGCTGCCCCGGCT
AGTGCCCCCGCTGGTGCCGATGACGATGACGATGACGATGGTGCTGGCGGAGGCGGTGGCGGTAGACGTGCTGAGGC
TGGACGTGTTGCTGTTGAATGCCTGGCTGCCTGTAGAGGAATCTTGGAGGCTCTGGCCGAGGGATTCGACGGAGACT
TGGCGGCTGTACCGGGACTGGCGGGAGCGAGGCCTGCCGCTCCACCTCGCCCCGGTCCTGCTGGTGCTGCCGCTCCT
CCTCATGCCGACGCTCCTAGACTCCGTGCTTGGCTCCGTGAACTCCGTTTCGTTCGTGACGCTTTGGTTCTGATGAG
ACTGAGAGGCGACTTGAGAGTGGCTGGAGGATCCGAGGCTGCTGTTGCTGCTGTCCGTGCTGTTTCTTTGGTTGCTG
GTGCTTTGGGCCCTGCTTTGCCGAGATCTCCCCGTTTGTTGTCGAGTGCCGCCGCTGCTGCCGCCGATTTGTTGTTC
CAAAACCAATCCCTCCGCCCTCTGCTCGCCGACACTGTTGCCGCTGCCGATTCTCTGGCTGCTCCGGCTTCTGCCCC
ACGTGAAGCTCGTAAACGTAAATCACCCGCTCCGGCTCGTGCTCCCCCTGGTGGCGCCCCTAGACCCCCTAAAAAAT
CCCGTGCCGATGCCCCTAGACCTGCTGCTGCTCCCCCCGCTGGTGCTGCTCCCCCCGCTCCCCCTACTCCCCCCCCA
CGCCCACCTCGTCCCGCTGCCCTCACACGCCGTCCTGCTGAGGGACCCGATCCACAAGGCGGCTGGCGTAGACAACC
TCCTGGCCCATCCCATACACCGGCACCATCTGCCGCTGCTTTGGAGGCTTACTGTGCTCCTCGTGCTGTGGCTGAAC
TCACCGATCATCCGCTGTTCCCTGCTCCCTGGCGTCCCGCCCTCATGTTCGATCCTAGAGCTTTGGCTTCCTTGGCC
GCTCGTTGTGCTGCCCCTCCCCCTGGCGGTGCTCCGGCTGCTTTCGGTCCTCTCCGTGCCTCTGGTCCACTCCGCCG
TGCCGCTGCCTGGATGAGACAAGTTCCCGACCCTGAGGATGTTAGAGTTGTGATCTTGTACTCGCCCTTGCCTGGCG
AGGATTTGGCCGCTGGTAGAGCTGGCGGTGGCCCCCCTCCTGAATGGTCTGCTGAACGTGGTGGTTTGTCTTGCTTG
TTGGCCGCCCTGGGAAACCGTCTGTGTGGTCCTGCTACTGCTGCTTGGGCTGGAAACTGGACTGGCGCTCCCGATGT
TTCTGCTCTCGGTGCTCAAGGAGTTTTGCTGCTCTCTACTCGTGACTTGGCATTCGCTGGAGCTGTTGAATTCCTGG
GACTCTTGGCTGGCGCTTGTGATAGGAGACTCATCGTCGTAAACGCTGTGAGAGCTGCCGATTGGCCTGCCGATGGT
CCTGTTGTGTCTCGTCAACACGCTTACTTGGCTTGTGAAGTGTTGCCCGCTGTCCAATGTGCTGTTCGCTGGCCTGC
TGCTCGTGATCTGAGGCGTACTGTTCTGGCTAGTGGTCGTGTTTTCGGACCTGGTGTTTTCGCTCGTGTCGAAGCTG
CTCACGCTAGACTGTACCCCGATGCCCCACCCCTCCGTTTGTGTCGTGGAGCAAACGTTCGCTACCGTGTCCGTACT
CGTTTCGGACCCGATACTCTGGTTCCAATGTCCCCTCGTGAATACCGTCGTGCTGTTCTGCCTGCCCTCGATGGACG
TGCTGCCGCTTCTGGCGCTGGTGACGCTATGGCTCCTGGCGCTCCGGACTTCTGTGAGGATGAGGCTCACTCACATC
GTGCCTGTGCCCGCTGGGGACTGGGCGCTCCATTGAGGCCTGTATACGTGGCACTGGGCCGTGATGCTGTTAGAGGC
GGACCCGCTGAATTGAGAGGCCCTCGTCGTGAATTCTGTGCTAGGGCTCTGCTCGAACCCGATGGAGATGCTCCTCC
TTTGGTACTCCGTGACGACGCCGATGCTGGTCCTCCCCCACAAATTCGCTGGGCTAGTGCTGCTGGACGTGCTGGTA
CTGTATTGGCTGCTGCTGGCGGTGGCGTTGAAGTTGTTGGTACTGCCGCTGGACTCGCTACACCTCCCCGCCGTGAA
CCTGTAGACATGGATGCTGAACTCGAGGATGATGACGACGGATTGTTCGGAGAGTAATAG

SEQ ID NO: 40 = construct US6ΔTMR

ATGAAGTTCCTCGTGAACGTGGCCCTGGTGTTCATGGTGGTGTACATCAGCTACATCTACGCCAACCGTTGGAAGTA
CGCTCTGGCTGACCCATCCCTGAAGATGGCTGACCCCAACCGTTTCCGTGGCAAGAACCTGCCCGTGCTGGACCAGC
TGACCGACCCCCCTGGCGTGAAGCGTGTGTACCACATCCAGCCATCCCTCGAAGACCCCTTCCAGCCCCCCTCCATC
CCCATCACCGTGTACTACGCTGTGCTGGAACGCGCTTGCCGTTCCGTGCTGCTGCACGCTCCTTCCGAGGCTCCCCA
GATCGTGCGTGGTGCTTCCGACGAGGCTCGCAAGCACACCTACAACCTGACTATCGCTTGGTACAGGATGGGTGACA
ACTGCGCTATCCCTATCACCGTCATGGAATACACCGAGTGCCCCTACAACAAGTCCCTGGGCGTGTGCCCTATCCGT
ACCCAGCCCCGTTGGTCCTACTACGACTCCTTCAGCGCTGTGTCCGAGGACAACCTGGGTTTCCTGATGCACGCTCC
CGCTTTCGAGACTGCTGGCACCTACCTGCGTCTGGTCAAGATCAACGACTGGACCGAGATCACCCAGTTCATCCTGG
AACACCGTGCTCGTGCTTCGTGCAAGTACGCCCTGCCCCTGCGTATCCCTCCTGCTGCTTGCCTGACCTCCAAGGCT
TACCAGCAGGGCGTGACCGTGGACTCCATCGGCATGCTGCCCCGTTTCATCCCCGAGAACCAGCGTACCGTGGCTCT
GTACTCTCTGAAGATCGCTGGCTGGCACGGTCCTAAGCCCCCCTACACCTCCACTCTGCTGCCCCCTGAGCTGTCCG
ACACCACCAACGCTACTCAGCCCGAGTTGGTGCCTGAGGACCCCGAGGACTCCGCTCTGTTGGAGGACCCCGCTGGA
ACCGTGTCCTCCCAGATCCCCCCCAACTGGCACATCCCTTCCATCCAGGACGTGGCCCCTCACCACGCTCCAGCTGC
TCCCTCCAACCCCCGTCGTCGTGCTCAGATGGCTCCCAAGCGTCTGCGTCTGCCCCACATCCGTGACGACGACGCTC
CTCCATCCCACCAGCCCCTGTTCTACCACCACCACCATCACCACTAATAA

SEQ ID NO: 41 = RL1

ATGTCTCGTCGTCGTGGTCCTCGTCGTCGTGGTCCTCGTCGTCGTCCGCGTCCGGGTGCGCCGGCGGTACCACGCCC
GGGTGCGCCGGCAGTGCCGCGTCCAGGCGCACTGCCTACCGCGGACTCTCAAATGGTGCCGGCGTATGATTCTGGTA
CTGCCGTCGAATCTGCTCCGGCAGCGAGCTCCCTGCTGCGTCGTTGGCTGCTGGTCCCTCAGGCGGACGATTCCGAT
GACGCAGACTACGCGGGCAACGACGACGCGGAGTGGGCTAACAGCCCGCCAAGCGAGGGTGGTGGCAAAGCGCCGGA
GGCTCCGCACGCAGCGCCTGCCGCAGCGTGCCCGCCTCCGCCTCCTCGTAAAGAACGTGGCCCTCAACGTCCTCTGC
CGCCGCACCTGGCTCTGCGTCTGCGTACTACCACTGAGTACCTGGCGCGTCTGTCTCTGCGTCGTCGCCGTCCGCCG
GCTAGCCCGCCGGCCGATGCACCGCGTGGCAAAGTGTGCTTCTCTCCACGTGTTCAAGTTCGTCACCTGGTGGCTTG
GGAAACGGCTGCCCGTCTGGCTCGCCGTGGCAGCTGGGCACGTGAGCGCGCAGACCGTGACCGCTTCCGTCGCCGTG
TGGCGGCTGCTGAAGCCGTTATCGGCCCGTGCCTGGAACCTGAGGCTCGCGCTCGCGCGCGTGCGCGCGCTCGTGCC
CACGAAGATGGCGGTCCAGCAGAGGAAGAAGAGGCAGCTGCAGCAGCGCGCGGTAGCTCCGCGGCTGCGGGTCCAGG
TCGTCGTGCCGTA

SEQ ID NO: 42 = RL2

ATGTCGTACTACCATCACCATCACCATCACATGGAGCCACGTCCTGGTACTTCTTCTCGCGCTGATCCTGGTCCTGA
ACGTCCGCCACGCCAGACTCCGGGCACCCAGCCGGCCGCCCCTCACGCTTGGGGCATGCTGAACGATATGCAGTGGC

TGGCGTCCTCTGATTCCGAAGAGGAGACTGAGGTTGGTATCAGCGATGATGATCTGCACCGCGACTCTACCAGCGAA
GCAGGTTCCACTGACACCGAAATGTTTGAAGCGGGCCTGATGGATGCCGCGACCCCGCCGGCTCGTCCGCCGGCTGA
ACGTCAGGGTAGCCCTACGCCTGCGGATGCGCAAGGCTCTTGTGGTGGTGGTCCAGTAGGCGAAGAGGAGGCTGAGG
CCGGTGGCGGCGGTGATGTGTGTGCGGTTTGTACCGATGAAATCGCACCGCCGCTGCGTTGTCAGTCTTTCCCGTGC
CTGCACCCGTTTTGCATTCCGTGCATGAAAACCTGGATCCCGCTGCGCAACACTTGCCCGCTGTGCAACACTCCGGT
TGCTTATCTGATCGTTGGTGTAACCGCATCTGGTTCCTTTTCTACCATCCCGATTGTCAACGACCCACGTACGCGTG
TTGAGGCGGAGGCGGCTGTACGTGCGGGCACCGCGGTGGACTTTATCTGGACCGGTAACCCGCGCACCGCGCCACGC
TCCCTGTCTCTGGGTGGCCATACCGTTCGTGCTCTGAGCCCGACCCCACCTTGGCCAGGCACCGATGACGAAGACGA
CGATCTGGCTGACGTTGACTATGTTCCGCCGGCACCGCGTCGCGCACCACGCCGTGGTGGCGGTGGCGCCGGTGCGA
CGCGCGGTACCTCCCAGCCGGCAGCAACTCGCCCAGCACCGCCGGGTGCCCCGCGTTCTAGCAGCTCCGGTGGCGCA
CCGCTGCGTGCTGGCGTGGGTTCTGGTTCCGGTGGTGGTCCGGCCGTGGCGGCTGTCGTCCCGCGTGTGGCTTCTCT
GCCACCGGCAGCTGGTGGCGGTCGTGCTCAAGCTCGTCGTGTCGGCGAGGACGCAGCGGCTGCTGAGGGCCGTACTC
CACCGGCCCGTCAACCGCGCGCAGCACAGGAACCGCCGATCGTGATCTCCGATTCCCCGCCACCGAGCCCGCGTCGC
CCGGCGGGTCCGGGTCCGCTGTCTTTTGTATCCTCCAGCTCTGCTCAGGTAAGCAGCGGTCCTGGCGGTGGCGGCCT
GCCACAGTCCTCTGGTCGTGCTGCTCGTCCTCGTGCGGCGGTTGCTCCTCGTGTACGTTCTCCGCCACGCGCTGCTG
CCGCGCCGGTCGTTTCTGCCTCTGCTGACGCGGCAGGTCCGGCTCCGCCTGCAGTTCCGGTTGATGCACACCGTGCA
CCGCGCTCTCGTATGACCCAGGCGCAGACTGATACCCAGGCACAATCCCTGGGTCGCGCGGGTGCGACTGACGCTCG
TGGTAGCGGTGGTCCGGGCGCTGAAGGTGGCCCGGGTGTTCCACGCGGTACTAACACTCCGGGCGCTGCGCCACACG
CGGCTGAAGGTGCGGCTGCACGTCCGCGTAAACGTCGTGGTTCCGACAGCGGTCCGGCTGCAAGCAGCAGCGCGAGC
TCTTCCGCTGCGCCTCGCAGCCCGCTGGCGCCGCAGGGTGTTGGCGCCAAGCGTGCTGCTCCGCGTCGTGCACCGGA
CTCCGATTCTGGCGACCGCGGTCACGGCCCGCTGGCCCCTGCTAGCGCAGGCGCTGCGCCGCCATCCGCCAGCCCGT
CTTCTCAGGCAGCTGTGGCTGCGGCGTCCTCTTCTTCCGCTAGCAGCTCTTCCGCCTCTTCTAGCAGCGCGTCCTCT
AGCAGCGCATCTTCCTCTTCTGCTTCTTCTTCTAGCGCTTCTAGCTCTTCCGCGTCCTCTTCCGCTGGCGGTGCAGG
CGGCTCTGTTGCTTCCGCCAGCGGCGCAGGTGAGCGTCGTGAAACGAGCCTGGGCCCACGTGCTGCTGCACCGCGTG
GCCCGCGTAAGTGTGCGCGCAAGACCCGCCACGCTGAAGGCGGTCCGGAGCCGGGTGCGCGTGATCCGGCTCCGGGT
CTGACCCGTTACCTGCCGATTGCGGGTGTGTCCTCCGTTGTGGCACTGGCGCCGTATGTGAACAAAACTGTCACGGG
CGATTGCCTGCCTGTTCTGGACATGGAAACCGGTCATATCGGCGCTTACGTCGTTCTGGTTGACCAAACCGGCAACG
TGGCGGATCTGCTGCGTGCGGCCGCTCCGGCTTGGTCCCGTCGTACCCTGCTGCCGGAACATGCTCGCAACTGTGTA
CGCCCACCGGATTACCCAACCCCGCCGGCCTCCGAGTGGAACTCCCTGTGGATGACCCCGGTTGGTAACATGCTGTT
CGACCAGGGCACGCTGGTTGGTGCTCTGGACTTTCACGGCCTGCGCTCCCGTCACCCGTGGTCCCGTGAGCAAGGCG
CTCCGGCCCCTGCGGGCGATGCCCCGGCTGGCCACGGCGAGAGTACTAGAGGATCATAA

SEQ ID NO: 43 = construct UL36.3.4.1

ATGTCGTACTACCATCACCATCACCATCACGCCGCTCAACGTGCTAGGGGATCCTCTGAACGCTGGGCTGCTGGTGT
CGAGGCTGCTTTGGATAGAGTGGAGAACCGTGCCGAATTCGATGTTGTCGAGCTGAGGAGACTCCAAGCTTTGGCTG

GTACTCACGGCTACAACCCTCGTGATTTCCGTAAACGTGCCGAACAGGCTTTGGCGGCAAACGCTGAGGCCGTAACA
TTGGCTCTGGACACTGCCTTCGCTTTCAACCCATACACGCCCGAAAACCAACGTCATCCTATGCTCCCACCTCTCGC
TGCTATTCACCGCCTGGGATGGAGCGCTGCTTTCCATGCTGCTGCTGAAACTTACGCCGACATGTTCCGTGTCGATG
CCGAACCACTGGCTAGACTGCTCCGTATCGCTGAGGGACTGCTGGAGATGGCTCAAGCTGGCGACGGATTCATCGAT
TACCATGAGGCTGTCGGTAGACTGGCCGATGATATGACTTCTGTGCCCGGATTGAGGCGCTACGTTCCTTTCTTCCA
ACATGGCTACGCCGATTACGTGGAACTGAGAGATCGCCTGGATGCTATTAGGGCCGACGTCCATAGAGCACTCGGTG
GTGTTCCGCTGGATTTGGCGGCTGCTGCCGAACAAATTTCCGCTGCTCGTAACGATCCTGAGGCTACTGCTGAATTG
GTCCGTACTGGTGTAACATTGCCTTGCCCTAGTGAGGACGCTCTCGTGGCTTGTGCTGCTGCCCTGGAGAGAGTCGA
TCAATCTCCCGTGAAAAACACGGCTTACGCCGAATACGTTGCCTTCGTGACCCGTCAAGACACTGCTGAGACTAAAG
ACGCTGTGGTCCGTGCTAAACAACAACGTGCTGAGGCCACTGAACGTGTTATGGCTGGCCTGAGAGAGGCTCTGGCT
GCTAGAGAACGTCGTGCTCAAATTGAGGCTGAGGGATTGGCAAACCTGAAAACCATGCTCAAAGTCGTGGCTGTACC
CGCTACTGTTGCTAAAACTCTCGACCAGGCTCGTAGTGTTGCCGAAATTGCCGATCAAGTCGAAGTGTTGCTGGATC
AAACCGAAAAAACTCGTGAACTGGATGTGCCTGCTGTGATCTGGCTCGAACACGCCCAAAGAACATTCGAGACACAC
CCTTTGTCTGCCGCTCGTGGTGATGGTCCTGGACCCTTGGCTCGTCATGCTGGCCGCCTCGGTGCCCTCTTCGATAC
TCGTCGTAGAGTAGACGCCTTGAGGAGATCCCTGGAGGAGGCTGAGGCTGAATGGGACGAAGTTTGGGGACGCTTCG
GTAGAGTGAGGGGCGGAGCGTGGAAATCTCCGGAGGGATTCCGTGCAATGCATGAGCAACTGAGGGCCCTCCAAGAC
ACAACAAACACCGTGTCTGGCCTGAGGGCTCAACCTGCTTACGAACGCTTGTCTGCTCGCTACCAAGGAGTACTCGG
AGCGAAAGGCGCTGAGAGAGCTGAGGCTGTTGAGGAACTCGGTGCTCGTGTCACTAAACACACCGCTCTGTGTGCTA
GGCTGAGAGATGAGGTCGTCCGTAGAGTGCCTTGGGAAATGAACTTCGATGCTCTGGGAGGATTGTTGGCTGAGTTC
GATGCCGCTGCTGCCGATTTGGCACCTTGGGCTGTAGAGGAATTCCGTGGTGCTAGAGAACTCATTCAATACCGTAT
GGGCCTGTACTCTGCCTACGCTAGAGCTGGAGGACAAACTGGTGCTGGAGCTGAATCTGCTCCTGCTCCTTTGCTCG
TGGATCTGAGGGCTTTGGATGCTCGTGCTCGTGCTTCTTCTTCCCCTGAGGGACATGAAGTGGACCCACAACTGCTG
AGGAGGCGTGGAGAGGCTTACTTGAGAGCTGGCGGCGACCCTGGACCTCTCGTGCTCCGTGAAGCTGTTTCTGCTTT
GGACCTGCCATTCGCCACATCTTTCTTGGCCCCCGATGGAACTCCCCTCCAATACGCTTTGTGCTTCCCTGCCGTAA
CGGACAAACTCGGAGCTTTGCTCATGAGGCCCGAGGCCGCTTGTGTTAGACCTCCTTTGCCTACCGATGTGCTGGAA
TCTGCCCCAACTGTGACTGCCATGTACGTACTCACTGTGGTCAACCGCCTCCAACTGGCATTGAGTGATGCTCAAGC
GGCAAACTTCCAACTGTTCGGTCGTTTCGTTCGTCATAGGCAGGCAACCTGGGGAGCGTCAATGGATGCCGCCGCTG
AATTGTACGTTGCCCTGGTGGCTACAACTCTCACACGTGAATTCGGTTGTCGCTGGGCACAATTGGGATGGGCTAGT
GGAGCTGCTGCTCCTAGACCCCCACCTGGACCCCGTGGCTCACAACGTCACTGTGTGGCATTCAACGAGAACGATGT
CCTCGTCGCTTTGGTTGCCGGTGTTCCCGAACACATCTACAACTTCTGGCGCCTGGACTTGGTCCGTCAACACGAGT
ACATGCACCTCACACTGGAGCGTGCCTTCGAGGATGCTGCCGAGTCTATGCTCTTCGTTCAACGCCTCACTCCACAT
CCCGACGCTCGTATTAGAGTTCTGCCGACCTTCTTGGATGGTGGTCCTCCTACACGTGGTCTGTTGTTCGGAACCCG
CTTGGCGGACTGGCGTCGTGGTAAACTGTCTGAAACCGACCCATTGGCCCCATGGAGATCTGCTTTGGAACTCGGAA
CCCAACGTCGTGACGTGCCTGCTTTGGGAAAACTGTCCCCTGCTCAAGCTTTGGCCGCTGTGTCGGTACTGGGCCGT
ATGTGCTTGCCCTCGGCTGCCTTGGCTGCTTTGTGGACCTGTATGTTCCCCGACGACTACACTGAATACGACTCATT

CGACGCCCTCTTGGCGGCTCGCCTGGAATCGGGACAAACATTGGGACCTGCTGGCGGTAGAGAGGCTTCATTGTAAT
AG

SEQ ID NO: 44 = construct UL36.4.2.5

ATGTCGTACTACCATCACCATCACCATCACGAATACGACTCCTTCGACGCTTTGTTGGCTGCTAGACTGGAATCTGG
TCAAACCTTGGGACCCGCTGGCGGTAGAGAGGCTTCTTTGCCCGAGGCTCCTCATGCTTTGTACCGTCCAACCGGAC
AACATGTTGCTGTGTTGGCGGCTGCTACTCATAGAACCCCTGCTGCTCGTGTTACTGCTATGGACCTGGTCTTGGCG
GCCGTTTTGCTGGGCGCTCCTGTGGTGGTCGCTCTGAGAAACACTACTGCCTTCTCCCGTGAATCCGAATTGGAACT
GTGCCTCACCCTGTTCGATTCTCGTCCCGGCGGACCGGATGCTGCCCTGAGAGATGTGGTATCCTCCGACATTGAAA
CCTGGGCTGTGGGCTTGCTCCACACCGATTTGAACCCTATTGAGAACGCTTGCTTGGCGGCTCAACTGCCACGCTTG
TCTGCCCTCATTGCTGAACGTCCTTTGGCCGATGGACCCCCTTGTTTGGTGTTGGTGGACATTTCGATGACACCTGT
CGCTGTTTTGTGGGAGGCCCCTGAACCACCTGGCCCTCCCGATGTTCGTTTCGTCGGTAGCGAGGCCACTGAGGAAT
TGCCTTTCGTGGCTACTGCTGGTGATGTTTTGGCGGCGAGTGCTGCCGATGCCGATCCTTTCTTCGCTCGTGCTATC
CTGGGCCGTCCTTTCGATGCTTCTCTGCTCACTGGTGAACTGTTCCCTGGTCACCCCGTTTACCAACGTCCCCTGGC
GGATGAGGCTGGTCCTTCTGCTCCTACTGCCGCTCGTGATCCTAGAGATCTGGCTGGAGGCGACGGTGGATCCGGAC
CTGAGGATCCCGCTGCTCCACCTGCTAGACAGGCCGATCCTGGTGTTTTGGCTCCTACTCTGCTCACCGATGCTACT
ACTGGCGAACCTGTGCCACCCCGTATGTGGGCTTGGATTCATGGACTGGAGGAACTGGCTTCCGATGATGCCGGCGG
TCCTACCCCAAACCCTGCCCCGGCTTTGCTGCCCCCTCCTGCTACGGATCAATCTGTCCCCACTTCCCAATACGCCC
CTAGACCAATTGGCCCGGCTGCCACTGCTAGAGAAACTCGTCCTTCCGTTCCCCCTCAACAAAACACTGGTCGTGTC
CCTGTGGCTCCACGTGATGACCCTAGACCTTCCCCCCCCTACTCCTTCCCCCCCTGCCGATGCTGCTTTGCCACCTCC
TGCCTTCTCTGGTTCTGCTGCTGCTTTCTCCGCTGCTGTTCCACGTGTTCGTCGTTCTAGGCGTACTCGTGCCAAAT
CCCGTGCCCCTCGTGCTTCTGCCCCACCCGAGGGATGGCGTCCCCCCGCTTTGCCTGCCCCTGTTGCTCCTGTGGCG
GCTTCTGCTCGTCCCCCCGATCAACCTCCTACTCCCGAATCTGCTCCCCCGGCTTGGGTTTCCGCTCTGCCATTGCC
ACCCGGACCTGCTAGTGCTCGTGGTGCTTTCCCTGCTCCAACCTTGGCCCCTATTCCCCCACCCCCCGCTGAGGGAG
CTGTTGTTCCCGGTGGTGATCGTAGACGTGGTCGCCGTCAAACAACTGCTGGACCATCCCCTACACCGCCACGTGGC
CCGGCTGCTGGTCCTCCTCGTCGCCTCACTAGGCCTGCTGTTGCTAGTCTGTCCGCTTCTTTGAACTCTCTGCCTTC
CCCCCGTGATCCTGCCGATCATGCTGCTGCCGTTTCTGCTGCCGCCGCTGCCGTACCACCTTCACCTGGACTGGCTC
CCCCAACTTCTGCTGTCCAAACCTCTCCTCCTCCCTTGGCGCCTGGTCCTGTTGCCCCATCTGAACCTTTGTGTGGC
TGGGTTGTGCCTGGAGGCCCTGTTGCTAGACGTCCCCCACCCCAATCTCCGGCTACTAAACCGGCTGCTCGTACCCG
TATTAGGGCTCGTTCTGTGCCCCAACCACCCTTGCCCCAACCTCCACTGCCTCAACCCCCCTTGCCTCAACCCCCTC
TCCCCCAACCACCTCTGCCTCAACCTCCGCTGCCCCAACCTCCTTTGCCCCAACCTCCTTTGCCCCAACCTCCTTTG
CCCCAACCTCCGCTGCCCCAACCTCCGCTGCCACCTGTTACTCGTACACTCACTCCCCAATCTCGTGACTCTGTGCC
TACACCTGAGTCTCCAACTCACACAAACACCCACTTGCCCGTTAGTGCTGTGACTTCTTGGGCTTCGTCCCTGGCTC
TCCATGTGGATTCTGCCCCTCCCCCTGCTTCATTGCTCCAAACTCTCCACATTTCCTCCGATGATGAACACTCCGAC
GCCGACTCACTCCGCTTCTCCGATTCCGATGACACTGAGGCTCTCGATCCTTTGCCTCCTGAACCTCACTTGCCACC

TGCCGATGAACCCCCCGGACCTCTGGCTGCCGACCATCTCCAATCACCTCACTCACAATTCGGTCCTTTGCCCGTTC
AAGCGAACGCTGTTCTGTCTCGTCGTTACGTGAGATCAACTGGCCGTTCTGCCTTGGCTGTGCTCATTAGAGCTTGT
CGCCGTATCCAACAACAACTCCAGCGTACTAGGAGAGCACTCTTCCAACGCTCAAACGCCGTGCTCACATCACTCCA
CCATGTCCGTATGCTCTTGGGATAATAG

SEQ ID NO: 45 = US12

ATGTCTTGGGCTCTGAAAACCACCGACATGTTCCTGGACTCTTCTCGTTGCACCCACCGTACCTACGGTGACGTTTG
CGCTGAAATCCACAAACGTGAACGTGAAGACCGTGAAGCTGCTCGTACCGCTGTTACCGACCCGGAACTGCCGCTGC
TGTGCCCGCCGGACGTTCGTTCTGACCCGGCTTCTCGTAACCCGACCCAGCAGACCCGTGGTTGCGCTCGTTCTAAC
GAACGTCAGGACCGTGTTCTGGCTCCGTGA

SEQ ID NO: 46 = US4

ATGAAGTTCCTCGTGAACGTGGCCCTGGTGTTCATGGTGGTGTACATCAGCTACATCTACGCTAACCGTTGGGGTTC
CGGCGTGCCCGGTCCCATCAACCCCCCCAACTCCGACGTGGTGTTCCCCGGTGGTTCCCCCGTGGCTCAGTACTGCT
ACGCTTACCCCCGTCTGGACGACCCTGGTCCCCTGGGTTCTGCTGACGCTGGTCGTCAGGACCTGCCCCGTCGTGTC
GTGCGTCACGAGCCCCTGGGTCGTAGCTTCCTGACCGGTGGCCTGGTGCTGTTGGCTCCCCCTGTGCGCGGTTTCGG
TGCTCCCAACGCTACCTACGCTGCTCGTGTGACCTACTACCGTCTGACCCGTGCTTGCCGTCAGCCCATCCTGCTGC
GTCAGTACGGTGGTTGCCGTGGTGGAGAGCCCCCATCCCCCAAGACCTGCGGTTCTTACACCTACACCTACCAGGGT
GGTGGTCCCCCTACCCGTTACGCTCTGGTCAACGCTTCCCTGCTGGTGCCCATCTGGGACCGTGCTGCTGAGACTTT
CGAGTACCAGATCGAGCTGGGTGGCGAGCTGCACGTGGGTCTGCTGTGGGTGGAAGTGGGTGGAGAGGGTCCCGGTC
CTACCGCTCCTCCTCAGGCTGCTCGTGCTGAGGGTGGTCCTTGCGTGCCACCCGTGCCTGCTGGTCGTCCTTGGCGT
TCCGTGCCCCCCGTGTGGTACTCCGCTCCCAACCCCGGTTTCCGCGGTCTGCGTTTCCGTGAGCGTTGCCTGCCTCC
CCAGACCCCTGCTGCTCCTTCCGACCTGCCTCGTGTGGCTTTCGCTCCCCAGTCCCTGCTCGTGGGTATCACCGGTC
GTACCTTCATCCGTATGGCTCGTCCCACCGAGGACGTGGGTGTCCTGCCTCCTCACTGGGCTCCAGGTGCTCTGGAC
GACGGTCCCTACGCTCCCTTCCCCCCTCGTCCCCGTTTCCGTCGTCACCACCACCATCACCACTAATAA

SEQ ID NO: 117 = construct RS1.2

ATGTCGTACTACCATCACCATCACCATCACATGGTGCTGTACGGCGGGCTGGGCGACAGCCGCCCCGGCCTCTGGGG
GGCGCCCGAGGCGGAGGAGGCGCGGGCCCGGTTCGAGGCCTCGGGCGCCCCGGCGCCCGTGTGGGCGCCCGAGCTGG
GCGACGCGGCGCAGCAGTACGCCCTGATCACGCGGCTGCTGTACACGCCGGACGCGGAGGCGATGGGGTGGCTCCAG
AACCCGCGCGTGGCGCCCGGGGACGTGGCGCTGGACCAGGCCTGCTTCCGGATCTCGGGCGCGGCGCGCAACAGCAG
CTCCTTCATCTCCGGCAGCGTGGCGCGGGCCGTGCCCCACCTGGGGTACGCCATGGCGGCGGGCCGCTTCGGCTGGG

GCCTGGCGCACGTGGCGGCCGCCGTGGCCATGAGCCGCCGCTACGACCGCGCGCAGAAGGGCTTCCTGCTGACCAGC
CTGCGCCGCGCCTACGCGCCCCTGCTGGCGCGCGAGAACGCGGCGCTGACCGGGGCGCGGACCCCCGACGACGGCGG
CGACGCCAACCGCCGCGACGGCGACGACGCCCGCGGGAAGCCCGCCGCCGCCGCCCCGTTGCCGTCGGCGGCGG
CGTCGCCGGCCGACGAGCGCGCGGTGCCCGCCGGCTACGGCGCCGCGGGGGTGCTCGCCGCCCTGGGGCGCCTGAGC
GCCGCGCCCCGCCTCCGCGCCGGCCGGGGCCGACGACGACGACGACGACGACGACGGCGCCGGCGGTGGTGGCGGTGG
TGGCGGTGGTGGCGGCGGCCGGCGCGCGGAGGCGGGCCGCGTGGCCGTGGAGTGCCTGGCCGCCTGCCGCGGGATCC
TGGAGGCGCTGGCGGAGGGCTTCGACGGCGACCTGGCGGCCGTGCCGGGGCTGGCCGGAGCCCGGCCCGCCGCGCCC
CCGCGCCCGGGGCCCGCGGGCGCGGCCGCCCCGCCGCACGCCGACGCGCCCCGCCTGCGCGCCTGGCTGCGCGAGCT
GCGGTTCGTGCGCGACGCGCTGGTGCTGATGCGCCTGCGCGGGGACCTGCGCGTGGCCGGCGGCAGCGAGGCCGCCG
TGGCCGCCGTGCGCGCCGTGAGCCTGGTCGCCGGGGCCCTGGGCCCGGCGCTGCCGCGGAGCCCGCGCCTGCTGAGC
TCCGCCGCCGCCGCCGCCGCGGACCTGCTCTTCCAGAACCAGAGCCTGAGTACTAGAGGATCATAA

SEQ ID NO: 118 = UL1

ATGTCGTACTACCATCACCATCACCATCACATGGGGTTCGTCTGTCTGTTTGGGCTTGTCGTTATGGGAGCCTGGGG
GGCGTGGGGTGGGTCACAGGCAACCGAATATGTTCTTCGTAGTGTTATTGCCAAAGAGGTGGGGGACATACTAAGAG
TGCCTTGCATGCGGACCCCCGCGGACGATGTTTCTTGGCGCTACGAGGCCCCGTCCGTTATTGACTATGCCCGCATA
GACGGAATATTTCTTCGCTATCACTGCCCGGGGTTGGACACGTTTTTGTGGGATAGGCACGCCCAGAGGGCGTATCT
TGTTAACCCCTTTCTCTTTGCGGCGGGATTTTTGGAGGACTTGAGTCACTCTGTGTTTCCGGCCGACACCCAGGAAA
CAACGACGCGCCGGGCCCTTTATAAAGAGATACGCGATGCGTTGGGCAGTCGAAAACAGGCCGTCAGCCACGCACCC
GTCAGGGCCGGGTGTGTAAACTTTGACTACTCACGCACTCGCCGCTGCGTCGGGCGACGCGATTTACGGCCTGCCAA
CACCACGTCAACGTGGGAACCGCCTGTGTCGTCGGACGATGAAGCGAGCTCGCAGTCGAAGCCCCTCGCCACCCAGC
CGCCCGTCCTCGCCCTTTCGAACGCCCCCCCACGGCGGGTCTCCCCGACGCGAGGTCGGCGCCGGCATACTCGCCTC
CGACGCAACTGA

SEQ ID NO: 119 = construct UL1s

ATGAAGTTCCTCGTGAACGTGGCCCTGGTGTTCATGGTGGTGTACATCAGCTACATCTACGCCAACCGTTGGGGGTT
CGTCTGTCTGTTTGGGCTTGTCGTTATGGGAGCCTGGGGGGCGTGGGGTGGGTCACAGGCAACCGAATATGTTCTTC
GTAGTGTTATTGCCAAAGAGGTGGGGGACATACTAAGAGTGCCTTGCATGCGGACCCCCGCGGACGATGTTTCTTGG
CGCTACGAGGCCCCGTCCGTTATTGACTATGCCCGCATAGACGGAATATTTCTTCGCTATCACTGCCCGGGGTTGGA
CACGTTTTTGTGGGATAGGCACGCCCAGAGGGCGTATCTTGTTAACCCCTTTCTCTTTGCGGCGGGATTTTTGGAGG
ACTTGAGTCACTCTGTGTTTCCGGCCGACACCCAGGAAACAACGACGCGCCGGGCCCTTTATAAAGAGATACGCGAT
GCGTTGGGCAGTCGAAAACAGGCCGTCAGCCACGCACCCGTCAGGGCCGGGTGTGTAAACTTTGACTACTCACGCAC
TCGCCGCTGCGTCGGGCGACGCGATTTACGGCCTGCCAACACCACGTCAACGTGGGAACCGCCTGTGTCGTCGGACG

ATGAAGCGAGCTCGCAGTCGAAGCCCCTCGCCACCCAGCCGCCCGTCCTCGCCCTTTCGAACGCCCCCCCACGGCGG
GTCTCCCCGACGCGAGGTCGGCGCCGGCATACTCGCCTCCGACGCAACCATCACCATCACCATCACTGA

SEQ ID NO: 120 = construct UL19ΔTEV

ATGTCGTACTACCATCACCATCACCATCACATGGCCGCTCCTGCCCGCGACCCCCCGGGTTACCGGTACGCCGCGGC
CATGGTGCCCACCGGCTCCATCCTGAGTACGATCGAGGTGGCGTCCCACCGCAGACTCTTTGATTTTTTCGCCCGCG
TGCGCTCCGACGAAAACAGCCTGTATGACGTAGAGTTTGACGCCCTGCTGGGGTCCTACTGCAACACCCTGTCGCTC
GTGCGCTTTCTGGAGCTCGGCCTGTCCGTGGCGTGCGTGTGCACCAAGTTCCCGGAGCTGGCTTACATGAACGAAGG
GCGTGTGCAGTTCGAGGTCCACCAGCCCCTCATCGCCCGCGACGGCCCGCACCCCGTCGAGCAGCCCGTGCATAATT
ACATGACGAAGGTCATCGACCGCCGGGCCCTGAACGCCGCCTTCAGCCTGGCCACCGAGGCCATTGCCCTGCTCACG
GGGGAGGCCCTGGACGGGACGGGCATTAGCCTGCATCGCCAGCTGCGCGCCATCCAGCAGCTCGCGCGCAACGTCCA
GGCCGTCCTGGGGGCGTTTGAGCGCGGCACGGCCGACCAGATGCTGCACGTGCTGTTGGAGAAGGCGCCTCCCCTGG
CCCTGCTGTTGCCCATGCAACGATATCTCGACAACGGGCGCCTGGCGACCAGGGTTGCCCGGGCGACCCTGGTCGCC
GAGCTGAAGCGGAGCTTTTGCGACACGAGCTTCTTCCTGGGCAAGGCGGGCCATCGCCGCGAGGCCATCGAGGCCTG
GCTCGTGGACCTGACCACGGCGACGCAGCCGTCCGTGGCCGTGCCCCGCCTGACGCACGCCGACACGCGCGGGCGGC
CGGTCGACGGGGTGCTGGTCACCACCGCCGCCATCAAACAGCGCCTCCTGCAGTCCTTCCTGAAGGTGGAGGACACC
GAGGCCGACGTGCCGGTGACCTACGGCGAGATGGTCTTGAACGGGGCCAACCTCGTCACGGCGCTGGTGATGGGCAA
GGCCGTGCGGAGCCTGGACGACGTGGGCCGCCACCTGCTGGAGATGCAGGAGGAGCAACTCGAGGCGAACCGGGAGA
CGCTGGATGAACTCGAAAGCGCCCCCCAGACAACGCGCGTGCGCGCGGATCTGGTGGCCATAGGCGACAGGCTGGTC
TTCCTGGAGGCCCTGGAGAAGCGCATCTACGCCGCCACCAACGTGCCCTACCCCCTGGTGGGCGCCATGGACCTGAC
GTTCGTCCTGCCCCTGGGGCTGTTCAACCCGGCCATGGAGCGCTTCGCCGCGCACGCCGGGGACCTGGTGCCCGCCC
CCGGCCACCCGGAGCCCCGCGCGTTCCCTCCCCGGCAGCTGTTTTTTTGGGGAAAGGACCACCAGGTTCTGCGGCTG
TCCATGGAGAACGCGGTCGGGACCGTGTGTCATCCTTCGCTCATGAACATCGACGCGGCCGTCGGGGGCGTGAACCA
CGACCCCGTCGAGGCCGCGAATCCGTACGGGGCGTACGTCGCGGCCCCGGCCGGCCCCGGCGCGGACATGCAGCAGC
GTTTTCTGAACGCCTGGCGGCAGCGCCTCGCCCACGGCCGGGTCCGGTGGGTCGCCGAGTGCCAGATGACCGCGGAG
CAGTTCATGCAGCCCGACAACGCCAACCTGGCTCTGGAGCTGCACCCCGCGTTCGACTTCTTCGCGGGCGTGGCCGA
CGTCGAGCTTCCCGGCGGCGAAGTCCCCCCGGCCGGTCCGGGGGCGATCCAGGCCACCTGGCGCGTGGTCAACGGCA
ACCTGCCCCTGGCGCTGTGTCCGGTGGCGTTTCGTGACGCCCGGGGCCTGGAGCTCGGCGTTGGCCGCCACGCCATG
GCGCCGGCTACCATAGCCGCCGTCCGCGGGGCGTTCGAGGACCGCAGCTACCCGGCGGTGTTCTACCTGCTGCAAGC
CGCGATTCACGGCAGCGAGCACGTGTTCTGCGCCCTGGCGCGGCTCGTGACTCAGTGCATCACCAGCTACTGGAACA
ACACGCGATGCGCGGCGTTCGTGAACGACTACTCGCTGGTCTCGTACATCGTGACCTACCTCGGGGGCGACCTCCCC
GAGGAGTGCATGGCCGTGTATCGGGACCTGGTGGCCCACGTCGAGGCCCTGGCCCAGCTGGTGGACGACTTTACCCT
GCCGGGCCCGGAGCTGGGCGGGCAGGCTCAGGCCGAGCTGAATCACCTGATGCGCGACCCGGCGCTGCTGCCGCCCC
TCGTGTGGGACTGCGACGGCCTTATGCGACACGCGGCCCTGGACCGCCACCGAGACTGCCGGATTGACGCGGGGGAG
CACGAGCCCGTCTACGCGGCGGCGTGCAACGTGGCGACGGCCGACTTTAACCGCAACGACGGCCGGCTGCTGCACAA

CACCCAGGCCCGCGCGGCCGACGCCGCCGACGACCGGCCGCACCGGCCGGCCGACTGGACCGTCCACCACAAAATCT
ACTATTACGTGCTGGTGCCGGCCTTCTCGCGGGGGCGCTGCTGCACCGCGGGGGTCCGCTTCGACCGCGTGTACGCC
ACGCTGCAGAACATGGTGGTCCCGGAGATCGCCCCCGGCGAGGAGTGCCCGAGCGATCCCGTGACCGACCCCGCCCA
CCCGCTGCATCCCGCCAATCTGGTGGCCAACACGGTCAACGCCATGTTCCACAACGGGCGCGTCGTCGTCGACGGGC
CCGCCATGCTCACGCTGCAGGTGCTGGCGCACAACATGGCCGAGCGCACGACGGCGCTGCTGTGCTCCGCGGCGCCC
GACGCGGGCGCCAACACCGCGTCGACGGCCAACATGCGCATCTTCGACGGGGCGCTGCACGCCGGCGTGCTGCTCAT
GGCCCCCCAGCACCTGGACCACACCATCCAAAATGGCGAATACTTCTACGTCCTGCCCGTCCACGCGCTGTTTGCGG
GCGCCGACCACGTGGCCAACGCGCCCAACTTCCCCCCGGCCCTGCGCGACCTGGCGCGCCACGTCCCCCTGGTCCCC
CCGGCCCTGGGGGCCAACTACTTCTCCTCCATCCGCCAGCCCGTGGTGCAGCACGCCCGCGAGAGCGCGGCGGGGGA
GAACGCGCTGACCTACGCGCTCATGGCGGGGTACTTCAAGATGAGCCCCGTGGCCCTGTATCACCAGCTCAAGACGG
GCCTCCACCCCGGGTTCGGGTTCACCGTCGTGCGGCAGGACCGCTTCGTGACCGAGAACGTGCTGTTTTCCGAGCGC
GCGTCGGAGGCGTACTTTCTGGGCCAGCTCCAGGTGGCCCGCCACGAAACGGGCGGGGGGGTCAGCTTCACGCTCAC
CCAGCCGCGCGGAAACGTGGACCTGGGTGTGGGCTACACCGCCGTCGCGGCCACGGCCACCGTCCGCAACCCCGTTA
CGGACATGGGCAACCTCCCCCAAAACTTTTACCTCGGCCGCGGGGCCCCCCCGCTGCTAGACAACGCGGCCGCCGTG
TACCTGCGCAACGCGGTCGTGGCGGGAAACCGGCTGGGGCCGGCCCAGCCCCTCCCGGTCTTTGGCTGCGCCCAGGT
GCCGCGGCGCGCCGGCATGGACCACGGGCAGGATGCCGTGTGTGAGTTCATCGCCACCCCCGTGGCCACGGACATCA
ACTACTTTCGCCGGCCCTGCAACCCGCGGGGACGCGCGGCCGGCGGCGTGTACGCGGGGGACAAGGAGGGGGACGTC
ATAGCCCTCATGTACGACCACGGCCAGAGCGACCCGGCGCGGCCCTTCGCGGCCACGGCCAACCCGTGGGCGTCGCA
GCGGTTCTCGTACGGGGACCTGCTGTACAACGGGGCCTATCACCTCAACGGGGCCTCGCCCGTCCTCAGCCCCTGCT
TCAAGTTCTTCACCGCGGCCGACATCACGGCCAAACATCGCTGCCTGGAGCGTCTTATCGTGGAAACGGGATCGGCG
GTATCCACGGCCACCGCTGCCAGCGACGTGCAGTTTAAGCGCCCGCCGGGGTGCCGCGAGCTCGTGGAAGACCCGTG
CGGCCTGTTTCAGGAAGCCTACCCGATCACCTGCGCCAGCGACCCCGCCCTGCTACGCAGCGCCCGCGATGGGGAGG
CCCACGCGCGAGAGACCCACTTTACGCAGTATCTCATCTACGACGCCTCCCCGCTAAAGGGCCTGTCTCTGTAA

SEQ ID NO: 121 = construct RS1.1

ATGAGTGCCGAACAGCGTAAAAAGAAAAAAACCACCACCACGACCCAAGGACGTGGAGCTGAAGTTGCTATGGCGGA
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CCCCTACACCAAACCCCGATCGTAGACCGGCTGCTAGACCTGGATTCGGATGGCATGGAGGACCCGAGGAAAACGAG
GACGAGGCGGACGACGCCGCTGCCGACGCCGACGCCGATGAGGCTGCCCCTGCTTCTGGAGAGGCGGTAGACGAACC
TGCTGCCGATGGAGTTGTTAGCCCTAGGCAATTGGCTTTGTTGGCGAGCATGGTAGACGAGGCTGTGAGAACAATCC
CTTCCCCTCCCCCTGAACGTGATGGAGCACAAGAGGAGGCGGCTAGGAGTCCCTCACCACCCCGTACACCTTCTATG
AGAGCGGATTACGGCGAGGAAAACGACGACGACGACGATGATGATGACGACGATGATCGTGATGCCGGACGCTGGGT
TAGGGGACCTGAAACCACTTCTGCTGTCCGTGGAGCATACCCCGATCCTATGGCGAGTTTGAGCCCTAGACCACCTG
CCCCGAGGAGACACCACCACCACCACCATCATAGGCGTAGACGTGCTCCTAGACGTCGTTCTGCCGCTAGTGACTCT
TCCAAATCTGGCTCTTCTTCATCTGCCTCTTCCGCTTCATCTTCGGCCTCATCGTCCTCTTCGGCATCCGCTTCGAG

TAGTGATGATGATGATGACGACGACGCTGCTAGAGCCCCCGCTTCTGCTGCCGACCACGCTGCTGGCGGAACTTTGG
GAGCCGACGACGAGGAGGCGGGAGTTCCTGCTCGTGCCCCGGGAGCTGCTCCGAGGCCTTCTCCACCCCGTGCTGAA
CCTGCTCCGGCTAGAACACCGGCCGCTACTGCTGGTAGACTGGAGCGTAGACGTGCCCGTGCTGCTGTGGCTGGTAG
AGATGCTACTGGCCGCTTCACTGCTGGCCGTCCTAGACGTGTTGAACTGGACGCCGATGCTGCTTCTGGTGCTTTCT
ACGCCCGTTACCGTGATGGTTACGTGTCTGGTGAACCTTGGCCTGGCGCTGGTCCACCTCCGCCCGGACGTGTACTC
TACGGTGGATTGGGCGATTCTCGCCCTGGTCTGTGGGGCGCTCCG

SEQ ID NO: 122 = construct RS1.3.1

TCGAGTGCCGCCGCTGCTGCCGCCGATTTGTTGTTCCAAAACCAATCCCTCCGCCCTCTGCTCGCCGACACTGTTGC
CGCTGCCGATTCTCTGGCTGCTCCGGCTTCTGCCCCACGTGAAGCTCGTAAACGTAAATCACCCGCTCCGGCTCGTG
CTCCCCCTGGTGGCGCCCCTAGACCCCCTAAAAAATCCCGTGCCGATGCCCCTAGACCTGCTGCTGCTCCCCCCGCT
GGTGCTGCTCCCCCCGCTCCCCCTACTCCCCCCCCCACGCCCACCTCGTCCCGCTGCCCTCACACGCCGTCCTGCTGA
GGGACCCGATCCACAAGGCGGCTGGCGTAGACAACCTCCTGGCCCATCCCATACACCGGCACCATCTGCCGCTGCTT
TGGAGGCTTACTGTGCTCCTCGTGCTGTGGCTGAACTCACCGATCATCCGCTGTTCCCTGCTCCCTGGCGTCCCGCC
CTCATGTTCGATCCTAGAGCTTTGGCTTCCTTGGCCGCTCGTTGTGCTGCCCCTCCCCCTGGCGGTGCTCCGGCTGC
TTTCGGTCCTCTCCGTGCCTCTGGTCCACTCCGCCGTGCCGCTGCCTGGATGAGACAAGTTCCCGACCCTGAGGATG
TTAGAGTTGTGATCTTGTACTCGCCCTTGCCTGGCGAGGATTTGGCCGCTGGTAGAGCTGGCGGTGGCCCCCCTCCT
GAATGGTCTGCTGAACGTGGTGGTTTGTCTTGCTTGTTGGCCGCCCTGGGAAACCGTCTGTGTGGTCCTGCTACTGC
TGCTTGGGCTGGAAACTGGACTGGCGCTCCCGATGTTTCTGCTCTCGGTGCTCAA

SEQ ID NO: 123 = construct RS1.3.2

TGGGCTGGAAACTGGACTGGCGCTCCCGATGTTTCTGCTCTCGGTGCTCAAGGAGTTTTGCTGCTCTCTACTCGTGA
CTTGGCATTCGCTGGAGCTGTTGAATTCCTGGGACTCTTGGCTGGCGCTTGTGATAGGAGACTCATCGTCGTAAACG
CTGTGAGAGCTGCCGATTGGCCTGCCGATGGTCCTGTTGTGTCTCGTCAACACGCTTACTTGGCTTGTGAAGTGTTG
CCCGCTGTCCAATGTGCTGTTCGCTGGCCTGCTGCTCGTGATCTGAGGCGTACTGTTCTGGCTAGTGGTCGTGTTTT
CGGACCTGGTGTTTTCGCTCGTGTCGAAGCTGCTCACGCTAGACTGTACCCCGATGCCCCACCCCTCCGTTTGTGTC
GTGGAGCAAACGTTCGCTACCGTGTCCGTACTCGTTTCGGACCCGATACTCTGGTTCCAATGTCCCCTCGTGAATAC
CGTCGTGCTGTTCTGCCTGCCCTCGATGGACGTGCTGCCGCTTCTGGCGCTGGTGACGCTATGGCTCCTGGCGCTCC
GGACTTCTGTGAGGATGAGGCTCACTCACATCGTGCCTGTGCCCGCTGGGGACTGGGCGCTCCATTGAGGCCTGTAT
ACGTGGCACTGGGCCGTGATGCTGTTAGAGGCGGACCCGCTGAATTGAGAGGCCCTCGTCGTGAATTCTGTGCTAGG
GCTCTGCTCGAACCCGATGGAGATGCTCCTCCTTTGGTACTCCGTGACGACGCCGATGCTGGTCCTCCCCCACAAAT
TCGCTGGGCTAGTGCTGCTGGACGTGCTGGTACTGTATTGGCTGCTGCTGGCGGTGGCGTTGAAGTTGTTGGTACTG

CCGCTGGACTCGCTACACCTCCCCGCCGTGAACCTGTAGACATGGATGCTGAACTCGAGGATGATGACGACGGATTG
TTCGGAGAG

SEQ ID NO: 124 = construct RS1.3

TCGAGTGCCGCCGCTGCTGCCGCCGATTTGTTGTTCCAAAACCAATCCCTCCGCCCTCTGCTCGCCGACACTGTTGC
CGCTGCCGATTCTCTGGCTGCTCCGGCTTCTGCCCCACGTGAAGCTCGTAAACGTAAATCACCCGCTCCGGCTCGTG
CTCCCCCTGGTGGCGCCCCTAGACCCCCTAAAAAATCCCGTGCCGATGCCCCTAGACCTGCTGCTGCTCCCCCCGCT
GGTGCTGCTCCCCCCGCTCCCCCTACTCCCCCCCCCACGCCCACCTCGTCCCGCTGCCCTCACACGCCGTCCTGCTGA
GGGACCCGATCCACAAGGCGGCTGGCGTAGACAACCTCCTGGCCCATCCCATACACCGGCACCATCTGCCGCTGCTT
TGGAGGCTTACTGTGCTCCTCGTGCTGTGGCTGAACTCACCGATCATCCGCTGTTCCCTGCTCCCTGGCGTCCCGCC
CTCATGTTCGATCCTAGAGCTTTGGCTTCCTTGGCCGCTCGTTGTGCTGCCCCTCCCCCTGGCGGTGCTCCGGCTGC
TTTCGGTCCTCTCCGTGCCTCTGGTCCACTCCGCCGTGCCGCTGCCTGGATGAGACAAGTTCCCGACCCTGAGGATG
TTAGAGTTGTGATCTTGTACTCGCCCTTGCCTGGCGAGGATTTGGCCGCTGGTAGAGCTGGCGGTGGCCCCCCTCCT
GAATGGTCTGCTGAACGTGGTGGTTTGTCTTGCTTGTTGGCCGCCCTGGGAAACCGTCTGTGTGGTCCTGCTACTGC
TGCTTGGGCTGGAAACTGGACTGGCGCTCCCGATGTTTCTGCTCTCGGTGCTCAAGGAGTTTTGCTGCTCTCTACTC
GTGACTTGGCATTCGCTGGAGCTGTTGAATTCCTGGGACTCTTGGCTGGCGCTTGTGATAGGAGACTCATCGTCGTA
AACGCTGTGAGAGCTGCCGATTGGCCTGCCGATGGTCCTGTTGTGTCTCGTCAACACGCTTACTTGGCTTGTGAAGT
GTTGCCCGCTGTCCAATGTGCTGTTCGCTGGCCTGCTGCTCGTGATCTGAGGCGTACTGTTCTGGCTAGTGGTCGTG
TTTTCGGACCTGGTGTTTTCGCTCGTGTCGAAGCTGCTCACGCTAGACTGTACCCCGATGCCCCACCCCTCCGTTTG
TGTCGTGGAGCAAACGTTCGCTACCGTGTCCGTACTCGTTTCGGACCCGATACTCTGGTTCCAATGTCCCCTCGTGA
ATACCGTCGTGCTGTTCTGCCTGCCCTCGATGGACGTGCTGCCGCTTCTGGCGCTGGTGACGCTATGGCTCCTGGCG
CTCCGGACTTCTGTGAGGATGAGGCTCACTCACATCGTGCCTGTGCCCGCTGGGGACTGGGCGCTCCATTGAGGCCT
GTATACGTGGCACTGGGCCGTGATGCTGTTAGAGGCGGACCCGCTGAATTGAGAGGCCCTCGTCGTGAATTCTGTGC
TAGGGCTCTGCTCGAACCCGATGGAGATGCTCCTCCTTTGGTACTCCGTGACGACGCCGATGCTGGTCCTCCCCCAC
AAATTCGCTGGGCTAGTGCTGCTGGACGTGCTGGTACTGTATTGGCTGCTGCTGGCGGTGGCGTTGAAGTTGTTGGT
ACTGCCGCTGGACTCGCTACACCTCCCCGCCGTGAACCTGTAGACATGGATGCTGAACTCGAGGATGATGACGACGG
ATTGTTCGGAGAG

SEQ ID NO: 125 = construct RS1.4

ACTGCTGGCCGTCCTAGACGTGTTGAACTGGACGCCGATGCTGCTTCTGGTGCTTTCTACGCCCGTTACCGTGATGG
TTACGTGTCTGGTGAACCTTGGCCTGGCGCTGGTCCACCTCCGCCCGGACGTGTACTCTACGGTGGATTGGGCGATT
CTCGCCCTGGTCTGTGGGGCGCTCCGGAGGCTGAGGAGGCTAGAGCCCGTTTCGAGGCTTCTGGTGCCCCTGCTCCT
GTTTGGGCTCCTGAATTGGGCGACGCTGCTCAACAATACGCCCTCATCACACGCTTGCTGTACACTCCCGACGCCGA

GGCTATGGGATGGCTCCAAAACCCTAGAGTTGCCCCTGGTGATGTTGCTCTGGATCAGGCTTGTTTCCGTATCTCCG
GCGCTGCTCGTAACTCTTCTTCGTTCATCTCCGGTTCTGTGGCTAGAGCTGTGCCTCACTTGGGATACGCCATGGCC
GCTGGACGTTTCGGCTGGGGACTGGCTCATGTTGCTGCCGCTGTAGCAATGTCTAGACGCTACGACCGTGCTCAAAA
AGGATTCTTGCTCACGTCACTGAGGCGTGCTTACGCCCCTTTGTTGGCCCGTGAAAACGCTGCCCTCACTGGCGCCC
GTACCCCCGATGACGGTGGCGACGCCAACCGCCACGATGGTGATGATGCTAGAGGCAAACCCGCTGCCGCTGCTGCT
CCTTTGCCCTCTGCCGCCGCTTCCCCTGCCGATGAACGTGCTGTTCCTGCCGGTTACGGTGCCGCTGGTGTGTTGGC
TGCTTTGGGACGCTTGAGTGCTGCCCCGGCTAGTGCCCCCGCTGGTGCCGATGACGATGACGATGACGATGGTGCTG
GCGGAGGCGGTGGCGGTAGACGTGCTGAGGCTGGACGTGTTGCTGTTGAATGCCTGGCTGCCTGTAGAGGAATCTTG
GAGGCTCTGGCCGAGGGATTCGACGGAGACTTGGCGGCTGTACCGGGACTGGCGGGAGCGAGGCCTGCCGCTCCACC
TCGCCCCGGTCCTGCTGGTGCTGCCGCTCCTCCTCATGCCGACGCTCCTAGACTCCGTGCTTGGCTCCGTGAACTCC
GTTTCGTTCGTGACGCTTTGGTTCTGATGAGACTGAGAGGCGACTTGAGAGTGGCTGGAGGATCCGAGGCTGCTGTT
GCTGCTGTCCGTGCTGTTTCTTTGGTTGCTGGTGCTTTGGGCCCTGCTTTGCCGAGATCTCCCCGTTTGTTGTCGAG
TGCCGCCGCTGCTGCCGCCGATTTGTTGTTCCAAAACCAATCCCTCCGCCCTCTGCTCGCCGACACTGTTGCCGCTG
CCGATTCTCTGGCTGCTCCGGCTTCTGCCCCACGTGAAGCTCGTAAACGTAAATCACCCGCTCCGGCTCGTGCTCCC
CCTGGTGGCGCCCCTAGACCCCCTAAAAAATCCCGTGCCGATGCCCCTAGACCTGCTGCTGCTCCCCCCCGCTGGTGC
TGCTCCCCCCGCTCCCCCTACTCCCCCCCCCACGCCCACCTCGTCCCGCTGCCCTCACACGCCGTCCTGCTGAGGGAC
CCGATCCACAAGGCGGCTGGCGTAGACAACCTCCTGGCCCATCCCATACACCGGCACCATCTGCCGCTGCTTTGGAG
GCTTACTGTGCT

SEQ ID NO: 126 = construct RS1.5

GCCGCTGCCGATTCTCTGGCTGCTCCGGCTTCTGCCCCACGTGAAGCTCGTAAACGTAAATCACCCGCTCCGGCTCG
TGCTCCCCCTGGTGGCGCCCCTAGACCCCCTAAAAAATCCCGTGCCGATGCCCCTAGACCTGCTGCTGCTCCCCCCG
CTGGTGCTGCTCCCCCCGCTCCCCCTACTCCCCCCCCCACGCCCACCTCGTCCCGCTGCCCTCACACGCCGTCCTGCT
GAGGGACCCGATCCACAAGGCGGCTGGCGTAGACAACCTCCTGGCCCATCCCATACACCGGCACCATCTGCCGCTGC
TTTGGAGGCTTACTGTGCTCCTCGTGCTGTGGCTGAACTCACCGATCATCCGCTGTTCCCTGCTCCCTGGCGTCCCG
CCCTCATGTTCGATCCTAGAGCTTTGGCTTCCTTGGCCGCTCGTTGTGCTGCCCCTCCCCCTGGCGGTGCTCCGGCT
GCTTTCGGTCCTCTCCGTGCCTCTGGTCCACTCCGCCGTGCCGCTGCCTGGATGAGACAAGTTCCCGACCCTGAGGA
TGTTAGAGTTGTGATCTTGTACTCGCCCTTGCCTGGCGAGGATTTGGCCGCTGGTAGAGCTGGCGGTGGCCCCCCTC
CTGAATGGTCTGCTGAACGTGGTGGTTTGTCTTGCTTGTTGGCCGCCCTGGGAAACCGTCTGTGTGGTCCTGCTACT
GCTGCTTGGGCTGGAAACTGGACTGGCGCTCCCGATGTTTCTGCTCTCGGTGCTCAAGGAGTTTTGCTGCTCTCTAC
TCGTGACTTGGCATTCGCTGGAGCTGTTGAATTCCTGGGACTCTTGGCTGGCGCTTGTGATAGGAGACTCATCGTCG
TAAACGCTGTGAGAGCTGCCGATTGGCCTGCCGATGGTCCTGTTGTGTCTCGTCAACACGCTTACTTGGCTTGTGAA
GTGTTGCCCGCTGTCCAATGTGCTGTTCGCTGGCCTGCTGCTCGTGATCTGAGGCGTACTGTTCTGGCTAGTGGTCG
TGTTTTCGGACCTGGTGTTTTCGCTCGTGTCGAAGCTGCTCACGCTAGACTGTACCCCGATGCCCCACCCCTCCGTT

TGTGTCGTGGAGCAAACGTTCGCTACCGTGTCCGTACTCGTTTCGGACCCGATACTCTGGTTCCAATGTCCCCTCGT
GAATACCGTCGTGCTGTTCTGCCTGCCCTCGATGGACGTGCTGCCGCTTCTGGCGCTGGTGACGCTATGGCTCCTGG
CGCTCCGGACTTCTGTGAGGATGAGGCTCACTCACATCGTGCCTGTGCCCGCTGGGGACTGGGCGCTCCATTGAGGC
CTGTATACGTGGCACTGGGCCGTGATGCTGTTAGAGGCGGACCCGCTGAATTGAGAGGCCCTCGTCGTGAATTCTGT
GCTAGGGCTCTGCTCGAACCCGATGGAGATGCTCCTCCTTTGGTACTCCGTGACGACGCCGATGCTGGTCCTCCCCC
ACAAATTCGCTGGGCTAGTGCTGCTGGACGTGCTGGTACTGTATTGGCTGCTGCTGGCGGTGGCGTTGAAGTTGTTG
GTACTGCCGCTGGACTCGCTACACCTCCCCGCCGTGAACCTGTAGACATGGATGCTGAACTCGAGGATGATGACGAC
GGATTGTTCGGAGAG

SEQ ID NO: 127 = construct RS1.6

CACCACCACCACCACCATCATAGGCGTAGACGTGCTCCTAGACGTCGTTCTGCCGCTAGTGACTCTTCCAAATCTGG
CTCTTCTTCATCTGCCTCTTCCGCTTCATCTTCGGCCTCATCGTCCTCTTCGGCATCCGCTTCGAGTAGTGATGATG
ATGATGACGACGACGCTGCTAGAGCCCCCGCTTCTGCTGCCGACCACGCTGCTGGCGGAACTTTGGGAGCCGACGAC
GAGGAGGCGGGAGTTCCTGCTCGTGCCCCGGGAGCTGCTCCGAGGCCTTCTCCACCCCGTGCTGAACCTGCTCCGGC
TAGAACACCGGCCGCTACTGCTGGTAGACTGGAGCGTAGACGTGCCCGTGCTGCTGTGGCTGGTAGAGATGCTACTG
GCCGCTTCACTGCTGGCCGTCCTAGACGTGTTGAACTGGACGCCGATGCTGCTTCTGGTGCTTTCTACGCCCGTTAC
CGTGATGGTTACGTGTCTGGTGAACCTTGGCCTGGCGCTGGTCCACCTCCGCCCGGACGTGTACTCTACGGTGGATT
GGGCGATTCTCGCCCTGGTCTGTGGGGCGCTCCGGAGGCTGAGGAGGCTAGAGCCCGTTTCGAGGCTTCTGGTGCCC
CTGCTCCTGTTTGGGCTCCTGAATTGGGCGACGCTGCTCAACAATACGCCCTCATCACACGCTTGCTGTACACTCCC
GACGCCGAGGCTATGGGATGGCTCCAAAACCCTAGAGTTGCCCCTGGTGATGTTGCTCTGGATCAGGCTTGTTTCCG
TATCTCCGGCGCTGCTCGTAACTCTTCTTCGTTCATCTCCGGTTCTGTGGCTAGAGCTGTGCCTCACTTGGGATACG
CCATGGCCGCTGGACGTTTCGGCTGGGGACTGGCTCATGTTGCTGCCGCTGTAGCAATGTCTAGACGCTACGACCGT
GCTCAAAAAGGATTCTTGCTCACGTCACTGAGGCGTGCTTACGCCCCTTTGTTGGCCCGTGAAAACGCTGCCCTCAC
TGGCGCCCGTACCCCCGATGACGGTGGCGACGCCAACCGCCACGATGGTGATGATGCTAGAGGCAAACCCGCTGCCG
CTGCTGCTCCTTTGCCCTCTGCCGCCGCTTCCCCTGCCGATGAACGTGCTGTTCCTGCCGGTTACGGTGCCGCTGGT
GTGTTGGCTGCTTTGGGACGCTTGAGTGCTGCCCCGGCTAGTGCCCCCGCTGGTGCCGATGACGATGACGATGACGA
TGGTGCTGGCGGAGGCGGTGGCGGTAGACGTGCTGAGGCTGGACGTGTTGCTGTTGAATGCCTGGCTGCCTGTAGAG
GAATCTTGGAGGCTCTGGCCGAGGGATTCGACGGAGACTTGGCGGCTGTACCGGGACTGGCGGGAGCGAGGCCTGCC
GCTCCACCTCGCCCCGGTCCTGCTGGTGCTGCCGCTCCTCCTCATGCCGACGCTCCTAGACTCCGTGCTTGGCTCCG
TGAACTCCGTTTCGTTCGTGACGCTTTGGTTCTGATGAGACTGAGAGGCGACTTGAGAGTGGCTGGAGGATCCGAGG
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TGCCGCTGCCGATTCTCTGGCTGCTCCGGCTTCTGCCCCACGTGAAGCTCGTAAACGTAAATCACCCGCTCCGGCTC
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GCTGGTGCTGCTCCCCCCGCTCCCCCTACTCCCCCCCCACGCCCACCTCGTCCCGCTGCCCTCACACGCCGTCCTGC
TGAGGGACCCGATCCACAAGGCGGCTGGCGTAGACAACCTCCTGGCCCATCCCATACACCGGCACCATCTGCCGCTG
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GCCCTCATGTTCGATCCTAGAGCTTTGGCTTCCTTGGCCGCTCGTTGTGCTGCCCCTCCCCCTGGCGGTGCTCCGGC
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AGTGTTGCCCGCTGTCCAATGTGCTGTTCGCTGGCCTGCTGCTCGTGATCTGAGGCGTACTGTTCTGGCTAGTGGTC
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TTGTGTCGTGGAGCAAACGTTCGCTACCGTGTCCGTACTCGTTTCGGACCCGATACTCTGGTTCCAATGTCCCCTCG
TGAATACCGTCGTGCTGTTCTGCCTGCCCTCGATGGACGTGCTGCCGCTTCTGGCGCTGGTGACGCTATGGCTCCTG
GCGCTCCGGACTTCTGTGAGGATGAGGCTCACTCACATCGTGCCTGTGCCCGCTGGGGACTGGGCGCTCCATTGAGG
CCTGTATACGTGGCACTGGGCCGTGATGCTGTTAGAGGCGGACCCGCTGAATTGAGAGGCCCTCGTCGTGAATTCTG
TGCTAGGGCTCTGCTCGAACCCGATGGAGATGCTCCTCCTTTGGTACTCCGTGACGACGCCGATGCTGGTCCTCCCC
CACAAATTCGCTGGGCTAGTGCTGCTGGACGTGCTGGTACTGTATTGGCTGCTGCTGGCGGTGGCGTTGAAGTTGTT
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SEQ ID NO: 128 = construct RS1.7

ATGAGTGCCGAACAGCGTAAAAAGAAAAAAACCACCACCACGACCCAAGGACGTGGAGCTGAAGTTGCTATGGCGGA
TGAGGATGGAGGCCGCTTGAGAGCTGCTGCTGAGACTACTGGAGGACCTGGATCACCGGACCCTGCCGATGGACCCC
CCCCTACACCAAACCCCGATCGTAGACCGGCTGCTAGACCTGGATTCGGATGGCATGGAGGACCCGAGGAAAACGAG
GACGAGGCGGACGACGCCGCTGCCGACGCCGACGCCGATGAGGCTGCCCCTGCTTCTGGAGAGGCGGTAGACGAACC
TGCTGCCGATGGAGTTGTTAGCCCTAGGCAATTGGCTTTGTTGGCGAGCATGGTAGACGAGGCTGTGAGAACAATCC
CTTCCCCTCCCCCTGAACGTGATGGAGCACAAGAGGAGGCGGCTAGGAGTCCCTCACCACCCCGTACACCTTCTATG
AGAGCGGATTACGGCGAGGAAAACGACGACGACGACGATGATGATGACGACGATGATCGTGATGCCGGACGCTGGGT
TAGGGGACCTGAAACCACTTCTGCTGTCCGTGGAGCATACCCCGATCCTATGGCGAGTTTGAGCCCTAGACCACCTG
CCCCGAGGAGACACCACCACCACCACCATCATAGGCGTAGACGTGCTCCTAGACGTCGTTCTGCCGCTAGTGACTCT
TCCAAATCTGGCTCTTCTTCATCTGCCTCTTCCGCTTCATCTTCGGCCTCATCGTCCTCTTCGGCATCCGCTTCGAG
TAGTGATGATGATGATGACGACGACGCTGCTAGAGCCCCCGCTTCTGCTGCCGACCACGCTGCTGGCGGAACTTTGG
GAGCCGACGACGAGGAGGCGGGAGTTCCTGCTCGTGCCCCGGGAGCTGCTCCGAGGCCTTCTCCACCCCGTGCTGAA
CCTGCTCCGGCTAGAACACCGGCCGCTACTGCTGGTAGACTGGAGCGTAGACGTGCCCGTGCTGCTGTGGCTGGTAG

AGATGCTACTGGCCGCTTCACTGCTGGCCGTCCTAGACGTGTTGAACTGGACGCCGATGCTGCTTCTGGTGCTTTCT
ACGCCCGTTACCGTGATGGTTACGTGTCTGGTGAACCTTGGCCTGGCGCTGGTCCACCTCCGCCCGGACGTGTACTC
TACGGTGGATTGGGCGCCCGTACCCCCGATGACGGTGGCGACGCCAACCGCCACGATGGTGATGATGCTAGAGGCAA
ACCCGCTGCCGCTGCTGCTCCTTTGCCCTCTGCCGCCGCTTCCCCTGCCGATGAACGTGCTGTTCCTGCCGGTTACG
GTGCCGCTGGTGTGTTGGCTGCTTTGGGACGCTTGAGTGCTGCCCCGGCTAGTGCCCCCGCTGGTGCCGATGACGAT
GACGATGACGATGGTGCTGGCGGAGGCGGTGGCGGTAGACGTGCTGAGGCTGGACGTGTTGCTGTTGAATGCCTGGC
TGCCTGTAGAGGAATCTTGGAGGCTCTGGCCGAGGGATTCGACGGAGACTTGGCGGCTGTACCGGGACTGGCGGGAG
CGAGGCCTGCCGCTCCACCTCGCCCCGGTCCTGCTGGTGCTGCCGCTCCTCCTCATGCCGACGCTCCTAGACTCCGT
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AGGATCCGAGGCTGCTGTTGCTGCTGTCCGTGCTGTTTCTTTGGTTGCTGGTGCTTTGGGCCCTGCTTTGCCGAGAT
CTCCCCGTTTGTTGTCGAGTGCCGCCGCTGCTGCCGCCGATTTGTTGTTCCAAAACCAATCCCTCCGCCCTCTGCTC
GCCGACACTGTTGCCGCTGCCGATTCTCTGGCTGCTCCGGCTTCTGCCCCACGTGAAGCTCGTAAACGTAAATCACC
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CTGCTCCCCCCGCTGGTGCTGCTCCCCCCGCTCCCCCTACTCCCCCCCCCACGCCCACCTCGTCCCGCTGCCCTCACA
CGCCGTCCTGCTGAGGGACCCGATCCACAAGGCGGCTGGCGTAGACAACCTCCTGGCCCATCCCATACACCGGCACC
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CCTGGCGTCCCGCCCTCATGTTCGATCCTAGAGCTTTGGCTTCCTTGGCCGCTCGTTGTGCTGCCCCTCCCCCTGGC
GGTGCTCCGGCTGCTTTCGGTCCTCTCCGTGCCTCTGGTCCACTCCGCCGTGCCGCTGCCTGGATGAGACAAGTTCC
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GCTGCTCTCTACTCGTGACTTGGCATTCGCTGGAGCTGTTGAATTCCTGGGACTCTTGGCTGGCGCTTGTGATAGGA
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TTGGCTTGTGAAGTGTTGCCCGCTGTCCAATGTGCTGTTCGCTGGCCTGCTGCTCGTGATCTGAGGCGTACTGTTCT
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CACCCCTCCGTTTGTGTCGTGGAGCAAACGTTCGCTACCGTGTCCGTACTCGTTTCGGACCCGATACTCTGGTTCCA
ATGTCCCCTCGTGAATACCGTCGTGCTGTTCTGCCTGCCCTCGATGGACGTGCTGCCGCTTCTGGCGCTGGTGACGC
TATGGCTCCTGGCGCTCCGGACTTCTGTGAGGATGAGGCTCACTCACATCGTGCCTGTGCCCGCTGGGGACTGGGCG
CTCCATTGAGGCCTGTATACGTGGCACTGGGCCGTGATGCTGTTAGAGGCGGACCCGCTGAATTGAGAGGCCCTCGT
CGTGAATTCTGTGCTAGGGCTCTGCTCGAACCCGATGGAGATGCTCCTCCTTTGGTACTCCGTGACGACGCCGATGC
TGGTCCTCCCCCACAAATTCGCTGGGCTAGTGCTGCTGGACGTGCTGGTACTGTATTGGCTGCTGCTGGCGGTGGCG
TTGAAGTTGTTGGTACTGCCGCTGGACTCGCTACACCTCCCCGCCGTGAACCTGTAGACATGGATGCTGAACTCGAG
GATGATGACGACGGATTGTTCGGAGAG

SEQ ID NO: 129 = construct RS1.8

ATGAGTGCCGAACAGCGTAAAAAGAAAAAAACCACCACCACGACCCAAGGACGTGGAGCTGAAGTTGCTATGGCGGA
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CCCCTACACCAAACCCCGATCGTAGACCGGCTGCTAGACCTGGATTCGGATGGCATGGAGGACCCGAGGAAAACGAG
GACGAGGCGGACGACGCCGCTGCCGACGCCGACGCCGATGAGGCTGCCCCTGCTTCTGGAGAGGCGGTAGACGAACC
TGCTGCCGATGGAGTTGTTAGCCCTAGGCAATTGGCTTTGTTGGCGAGCATGGTAGACGAGGCTGTGAGAACAATCC
CTTCCCCTCCCCCTGAACGTGATGGAGCACAAGAGGAGGCGGCTAGGAGTCCCTCACCACCCCGTACACCTTCTATG
AGAGCGGATTACGGCGAGGAAAACGACGACGACGACGATGATGATGACGACGATGATCGTGATGCCGGACGCTGGGT
TAGGGGACCTGAAACCACTTCTGCTGTCCGTGGAGCATACCCCGATCCTATGGCGAGTTTGAGCCCTAGACCACCTG
CCCCGAGGAGACACCACCACCACCACCATCATAGGCGTAGACGTGCTCCTAGACGTCGTTCTGCCGCTAGTGACTCT
TCCAAATCTGGCTCTTCTTCATCTGCCTCTTCCGCTTCATCTTCGGCCTCATCGTCCTCTTCGGCATCCGCTTCGAG
TAGTGATGATGATGATGACGACGACGCTGCTAGAGCCCCCGCTTCTGCTGCCGACCACGCTGCTGGCGGAACTTTGG
GAGCCGACGACGAGGAGGCGGGAGTTCCTGCTCGTGCCCCGGGAGCTGCTCCGAGGCCTTCTCCACCCCGTGCTGAA
CCTGCTCCGGCTAGAACACCGGCCGCTACTGCTGGTAGACTGGAGCGTAGACGTGCCCGTGCTGCTGTGGCTGGTAG
AGATGCTACTGGCCGCTTCACTGCTGGCCGTCCTAGACGTGTTGAACTGGACGCCGATGCTGCTTCTGGTGCTTTCT
ACGCCCGTTACCGTGATGGTTACGTGTCTGGTGAACCTTGGCCTGGCGCTGGTCCACCTCCGCCCGGACGTGTACTC
TACGGTGGATTGGGCGATTCTCGCCCTGGTCTGTGGGGCGCTCCGGAGGCTGAGGAGGCTAGAGCCCGTTTCGAGGC
TTCTGGTGCCCCTGCTCCTGTTTGGGCTCCTGAATTGGGCGACGCTGCTCAACAATACGCCCTCATCACACGCTTGC
TGTACACTCCCGACGCCGAGGCTATGGGATGGCTCCAAAACCCTAGAGTTGCCCCTGGTGATGTTGCTCTGGATCAG
GCTTGTTTCCGTATCTCCGGCGCTGCTCGTAACTCTTCTTCGTTCATCTCCGGTTCTGTGGCTAGAGCTGTGCCTCA
CTTGGGATACGCCATGGCCGCTGGACGTTTCGGCTGGGGACTGGCTCATGTTGCTGCCGCTGTAGCAATGTCTAGAC
GCTACGACCGTGCTCAAAAAGGATTCTTGCTCACGTCACTGAGGCGTGCTTACGCCCCTTTGTTGGCCCGTGAAAAC
GCTGCCCTCACTGGCGCCCGTACCCCCGATGACGGTGGCGACGCCAACCGCCACGATGGTGATGATGCTAGAGGCAA
ACCCGCTGCCGCTGCTGCTCCTTTGCCCTCTGCCGCCGCTTCCCCTGCCGATGAACGTGCTGTTCCTGCCGGTTACG
GTGCCGCTGGTGTGTTGGCTGCTTTGGGACGCTTGAGTGCTGCCCCGGCTAGTGCCCCCGCTGGTGCCGATGACGAT
GACGATGACGATGGTGCTGGCGGAGGCGGTGGCGGTAGACGTGCTGAGGCTGGACGTGTTGCTGTTGAATGCCTGGC
TGCCTGTAGAGGAATCTTGGAGGCTCTGGCCGAGGGATTCGACGGAGACTTGGCGGCTGTACCGGGACTGGCGGGAG
CGAGGCCTGCCGCTCCACCTCGCCCCGGTCCTGCTGGTGCTGCCGCTCCTCCTCATGCCGACGCTCCTAGACTCCGT
GCTTGGCTCCGTGAACTCCGTTTCGTTCGTGACGCTTTGGTTCTGATGAGACTGAGAGGCGACTTGAGAGTGGCTGG
AGGATCCGAGGCTGCTGTTGCTGCTGTCCGTGCTGTTTCTTTGGTTGCTGGTGCTTTGGGCCCTGCTTTGCCGAGAT
CTCCCCGTTTGTTGTCGAGTGCCGCCGCTGCTGCCGCCGATTTGTTGTTCCAAAACCAATCCCTCCGCCCTCTGCTC
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TTACTGTGCTCCTCGTGCTGTGGCTGAACTCACCGATCATCCGCTGTTCCCTGCTCCCTGGCGTCCCGCCCTCATGT
TCGATCCTAGAGCTTTGGCTTCCTTGGCCGCTCGTTGTGCTGCCCCTCCCCCTGGCGGTGCTCCGGCTGCTTTCGGT
CCTCTCCGTGCCTCTGGTCCACTCCGCCGTGCCGCTGCCTGGATGAGACAAGTTCCCGACCCTGAGGATGTTAGAGT
TGTGATCTTGTACTCGCCCTTGCCTGGCGAGGATTTGGCCGCTGGTAGAGCTGGCGGTGGCCCCCCTCCTGAATGGT
CTGCTGAACGTGGTGGTTTGTCTTGCTTGTTGGCCGCCCTGGGAAACCGTCTGTGTGGTCCTGCTACTGCTGCTTGG

GCTGGAAACTGGACTGGCGCTCCCGATGTTTCTGCTCTCGGTGCTCAAGGAGTTTTGCTGCTCTCTACTCGTGACTT
GGCATTCGCTGGAGCTGTTGAATTCCTGGGACTCTTGGCTGGCGCTTGTGATAGGAGACTCATCGTCGTAAACGCTG
TGAGAGCTGCCGATTGGCCTGCCGATGGTCCTGTTGTGTCTCGTCAACACGCTTACTTGGCTTGTGAAGTGTTGCCC
GCTGTCCAATGTGCTGTTCGCTGGCCTGCTGCTCGTGATCTGAGGCGTACTGTTCTGGCTAGTGGTCGTGTTTTCGG
ACCTGGTGTTTTCGCTCGTGTCGAAGCTGCTCACGCTAGACTGTACCCCGATGCCCCACCCCTCCGTTTGTGTCGTG
GAGCAAACGTTCGCTACCGTGTCCGTACTCGTTTCGGACCCGATACTCTGGTTCCAATGTCCCCTCGTGAATACCGT
CGTGCTGTTCTGCCTGCCCTCGATGGACGTGCTGCCGCTTCTGGCGCTGGTGACGCTATGGCTCCTGGCGCTCCGGA
CTTCTGTGAGGATGAGGCTCACTCACATCGTGCCTGTGCCCGCTGGGGACTGGGCGCTCCATTGAGGCCTGTATACG
TGGCACTGGGCCGTGATGCTGTTAGAGGCGGACCCGCTGAATTGAGAGGCCCTCGTCGTGAATTCTGTGCTAGGGCT
CTGCTCGAACCCGATGGAGATGCTCCTCCTTTGGTACTCCGTGACGACGCCGATGCTGGTCCTCCCCCACAAATTCG
CTGGGCTAGTGCTGCTGGACGTGCTGGTACTGTATTGGCTGCTGCTGGCGGTGGCGTTGAAGTTGTTGGTACTGCCG
CTGGACTCGCTACACCTCCCCGCCGTGAACCTGTAGACATGGATGCTGAACTCGAGGATGATGACGACGGATTGTTC
GGAGAG

SEQ ID NO: 130 = His tag

HHHHHH

SEQ ID NO: 131 = Tag

MSYYHHHHHH

SEQ ID NO: 132 = Secretion Signal

MKFLVNVALVFMVVYISYIYA

SEQ ID NO: 133 = UL49.5

ATGTCGTACTACCATCACCATCACCATCACATGACGGGGAAACCCGCAAGACTGGGCCGCTGGGTGGTGCTGTTGTT
CGTCGCGCTCGTCGCGGGCGTGCCCGGGGAGCCGCCGAACGCGGCAGGCGCACGCGGCGTTATCGGGGACGCGCAAT
GCCGGGGCGACAGCGCCGGTGTGGTGTCCGTCCCGGGGGTCCTGGTGCCCTTTTATCTAGGCATGACCTCGATGGGC
GTATGTATGATCGCGCACGTGTATCAGATATGCCAGCGGGCACTGGCCGCCGGGTCAGCCTGA

SEQ ID NO: 134 = UL10

ATGGGACGCCGGGCCCCCAGGGGATCCCCCGAGGCCGCGCCGGGCGCCGACGTCGCGCCCGGGGCGCGGGCGGCGTG
GTGGGTCTGGTGTGTGCAGGTGGCGACGTTCATCGTCTCGGCCATCTGCGTCGTGGGGCTCCTGGTGCTGGCCTCTG
TGTTCCGGGACAGGTTTCCCTGCCTTTACGCCCCCGCGACCTCTTATGCGAAGGCGAACGCCACGGTCGAGGTGCGC
GGGGGTGTAGCCGTCCCCCTCCGGTTGGACACGCAGAGCCTGCTGGCCACGTACGCAATTACGTCTACGCTGTTGCT
GGCGGCGGCCGTGTACGCCGCGGTGGGCGCGGTGACCTCGCGCTACGAGCGCGCGCTGGATGCGGCCCGTCGCCTGG
CGGCGGCCCGTATGGCGATGCCACACGCCACGCTAATCGCCGGAAACGTCTGCGCGTGGCTGTTGCAGATCACAGTC
CTGCTGCTGGCCCACCGCATCAGCCAGCTGGCCCACCTTATCTACGTCCTGCACTTTGCGTGCCTCGTGTATCTCGC
GGCCCATTTTTGCACCAGGGGGGTCCTGAGCGGGACGTACCTGCGTCAGGTTCACGGCCTGATTGACCCGGCGCCGA
CGCACCATCGTATCGTCGGTCCGGTGCGGGCAGTAATGACAAACGCCTTATTACTGGGCACCCTCCTGTGCACGGCC
GCCGCCGCGGTCTCGTTGAACACGATCGCCGCCCTGAACTTCAACTTTTCCGCCCCGAGCATGCTCATCTGCCTGAC
GACGCTGTTCGCCCTGCTTGTCGTGTCGCTGTTGTTGGTGGTCGAGGGGGTGCTGTGTCACTACGTGCGCGTGTTGG
TGGGCCCCCACCTCGGGGCCATCGCCGCCACCGGCATCGTCGGCCTGGCCTGCGAGCACTACCACACCGGTGGTTAC
TACGTGGTGGAGCAGCAGTGGCCGGGGGCCCAGACGGGAGTCCGCGTCGCCCTGGCGCTCGTCGCCGCCTTTGCCCT
CGCCATGGCCGTGCTTCGGTGCACGCGCGCCTACCTGTATCACCGGCGACACCACACTAAATTTTTCGTGCGCATGC
GCGACACCCGGCACCGCGCCCATTCGGCGCTTCGACGCGTACGCAGCTCCATGCGCGGTTCTAGGCGTGGCGGGCCG
CCCGGAGACCCGGGCTACGCGGAAACCCCCTACGCGAGCGTGTCCCACCACGCCGAGATCGACCGGTATGGGGATTC
CGACGGGGACCCGATCTACGACGAAGTGGCCCCCGACCACGAGGCCGAGCTCTACGCCCGAGTGCAACGCCCCGGGC
CTGTGCCCGACGCCGAGCCCATTTACGACACCGTGGAGGGGTATGCGCCAAGGTCCGCGGGGGAGCCGGTGTACAGC
ACCGTTCGGCGATGGTAG

SEQ ID NO: 135 = uracil DNA glycosylase encoded by UL2

MKRARSRSPSPPSRPSSPFRTPPHGGSPRREVGAGILASDATSHVCIASHPGSGAGQPTRLAAGSAVQRRRPRGCPP
GVMFSASTTPEQPLGLSGDATPPLPTSVPLDWAAFRRAFLIDDAWRPLLEPELANPLTARLLAEYDRRCQTEEVLPP
REDVFSWTRYCTPDDVRVVIIGQDPYHHPGQAHGLAFSVRADVPVPPSLRNVLAAVKNCYPDARMSGRGCLEKWARD
GVLLLNTTLTVKRGAAASHSKLGWDRFVGGVVQRLAARRPGLVFMLWGAHAQNAIRPDPRQHYVLKFSHPSPLSKVP
FGTCQHFLAANRYLETRDIMPIDWSV

SEQ ID NO: 136 = gL2 secreted v.2 encoded by construct UL1s v.2

AGSQATEYVLRSVIAKEVGDILRVPCMRTPADDVSWRYEAPSVIDYARIDGIFLRYHCPGLDTFLWDRHAQRAYLVN
PFLFAAGFLEDLSHSVFPADTQETTTRRALYKEIRDALGSRKQAVSHAPVRAGCVNFDYSRTRRCVGRRDLRPANTT
STWEPPVSSDDEASSQSKPLATQPPVLALSNAPPRRVSPTRGRRRHTRLRRN

SEQ ID NO: 137 = UL1s v.2

ATGAAGTTCCTCGTGAACGTGGCCCTGGTGTTCATGGTGGTGTACATCAGCTACATCTACGCCGCCGGGTCACAGGC
AACCGAATATGTTCTTCGTAGTGTTATTGCCAAAGAGGTGGGGGGACATACTAAGAGTGCCTTGCATGCGGACCCCCG
CGGACGATGTTTCTTGGCGCTACGAGGCCCCGTCCGTTATTGACTATGCCCGCATAGACGGAATATTTCTTCGCTAT
CACTGCCCGGGGTTGGACACGTTTTTGTGGGATAGGCACGCCCAGAGGGCGTATCTTGTTAACCCCTTTCTCTTTGC
GGCGGGATTTTTGGAGGACTTGAGTCACTCTGTGTTTCCGGCCGACACCCAGGAAACAACGACGCGCCGGGCCCTTT
ATAAAGAGATACGCGATGCGTTGGGCAGTCGAAAACAGGCCGTCAGCCACGCACCCGTCAGGGCCGGGTGTGTAAAC
TTTGACTACTCACGCACTCGCCGCTGCGTCGGGCGACGCGATTTACGGCCTGCCAACACCACGTCAACGTGGGAACC
GCCTGTGTCGTCGGACGATGAAGCGAGCTCGCAGTCGAAGCCCCTCGCCACCCAGCCGCCCGTCCTCGCCCTTTCGA
ACGCCCCCCCACGGCGGGTCTCCCCGACGCGAGGTCGGCGCCGGCATACTCGCCTCCGACGCAACCATCACCATCAC
CATCACTGA

SEQ ID NO: 138 = ICP4 internal fragment encoded by construct RS1.9 (deletion of #391-544 and #786-821)

MSAEQRKKKKTTTTTQGRGAEVAMADEDGGRLRAAAETTGGPGSPDPADGPPPTPNPDRRPAARPGFGWHGGPEENE
DEADDAAADADADEAAPASGEAVDEPAADGVVSPRQLALLASMVDEAVRTIPSPPPERDGAQEEAARSPSPPRTPSM
RADYGEENDDDDDDDDDDDRDAGRWVRGPETTSAVRGAYPDPMASLSPRPPAPRRHHHHHHHRRRRAPRRRSAASDS
SKSGSSSSASSASSSASSSSSASASSSDDDDDDDAARAPASAADHAAGGTLGADDEEAGVPARAPGAAPRPSPPRAE
PAPARTPAATAGRLERRRARAAVAGRDATGRFTAGRPRRVELDADAASGAFYARYRDGYVSGEPWPGAGPPPPGRVL
YGGLGRTPDDGGDANRHDGDDARGKPAAAAAPLPSAAASPADERAVPAGYGAAGVLAALGRLSAAPASAPAGADDDD
DDDGAGGGGGGRRAEAGRVAVECLAACRGILEALAEGFDGDLAAVPGLAGARPAAPPRPGPAGAAAPPHADAPRLRA
WLRELRFVRDALVLMRLRGDLRVAGGSEAAVAAVRAVSLVAGALGPALPRSPRLLSSAAAAAADLLFQNQSLRPLLA
DTVAAADSLAAPASAAAPPAGAAPPAPPTPPPRPPRPAALTRRPAEGPDPQGGWRRQPPGPSHTPAPSAAALEAYCA
PRAVAELTDHPLFPAPWRPALMFDPRALASLAARCAAPPPGGAPAAFGPLRASGPLRRAAAWMRQVPDPEDVRVVIL
YSPLPGEDLAAGRAGGGPPPEWSAERGGLSCLLAALGNRLCGPATAAWAGNWTGAPDVSALGAQGVLLLSTRDLAFA
GAVEFLGLLAGACDRRLIVVNAVRAADWPADGPVVSRQHAYLACEVLPAVQCAVRWPAARDLRRTVLASGRVFGPGV
FARVEAAHARLYPDAPPLRLCRGANVRYRVRTRFGPDTLVPMSPREYRRAVLPALDGRAAASGAGDAMAPGAPDFCE
DEAHSHRACARWGLGAPLRPVYVALGRDAVRGGPAELRGPRREFCARALLEPDGDAPPLVLRDDADAGPPPQIRWAS
AAGRAGTVLAAAGGGVEVVGTAAGLATPPRREPVDMDAELEDDDDGLFGE

SEQ ID NO: 139 = ICP4 internal fragment encoded by construct RS1.10 (deletion of # 391-508 and #786-821)

MSAEQRKKKKTTTTTQGRGAEVAMADEDGGRLRAAAETTGGPGSPDPADGPPPTPNPDRRPAARPGFGWHGGPEENE
DEADDAAADADADEAAPASGEAVDEPAADGVVSPRQLALLASMVDEAVRTIPSPPPERDGAQEEAARSPSPPRTPSM
RADYGEENDDDDDDDDDDDRDAGRWVRGPETTSAVRGAYPDPMASLSPRPPAPRRHHHHHHHRRRRAPRRRSAASDS
SKSGSSSSASSASSSASSSSSASASSSDDDDDDDAARAPASAADHAAGGTLGADDEEAGVPARAPGAAPRPSPPRAE
PAPARTPAATAGRLERRRARAAVAGRDATGRFTAGRPRRVELDADAASGAFYARYRDGYVSGEPWPGAGPPPPGRVL
YGGLGAMSRRYDRAQKGFLLTSLRRAYAPLLARENAALTGARTPDDGGDANRHDGDDARGKPAAAAAPLPSAAASPA
DERAVPAGYGAAGVLAALGRLSAAPASAPAGADDDDDDDGAGGGGGGRRAEAGRVAVECLAACRGILEALAEGFDGD
LAAVPGLAGARPAAPPRPGPAGAAAPPHADAPRLRAWLRELRFVRDALVLMRLRGDLRVAGGSEAAVAAVRAVSLVA
GALGPALPRSPRLLSSAAAAAADLLFQNQSLRPLLADTVAAADSLA**APASA**AAPPAGAAPPAPPTPPPRPPRPAALT
RRPAEGPDPQGGWRRQPPGPSHTPAPSAAALEAYCAPRAVAELTDHPLFPAPWRPALMFDPRALASLAARCAAPPPG
GAPAAFGPLRASGPLRRAAAWMRQVPDPEDVRVVILYSPLPGEDLAAGRAGGGPPPEWSAERGGLSCLLAALGNRLC
GPATAAWAGNWTGAPDVSALGAQGVLLLSTRDLAFAGAVEFLGLLAGACDRRLIVVNAVRAADWPADGPVVSRQHAY
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SEQ ID NO: 140 = construct RS1.9

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EQUIVALENTS AND SCOPE

[0448] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[0449] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Thus, for example, reference to “a cell” includes reference to one or more cells known to those skilled in the art, and so forth. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, etc., from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Furthermore, where the claims recite a

composition, it is to be understood that methods of using the composition for any of the purposes disclosed herein are included, and methods of making the composition according to any of the methods of making disclosed herein or other methods known in the art are included, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise.

[0450] Where elements are presented as lists, e.g., in Markush group format, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, etc., certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements, features, etc. For purposes of simplicity those embodiments have not been specifically set forth *in haec verba* herein. It is noted that the term "comprising" is intended to be open and permits the inclusion of additional elements or steps.

[0451] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0452] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (e.g., any antigen, any method of administration, any prophylactic and/or therapeutic application, etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[0453] The publications discussed above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be

construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior disclosure.

OTHER EMBODIMENTS

[0454] Those of ordinary skill in the art will readily appreciate that the foregoing represents merely certain preferred embodiments of the invention. Various changes and modifications to the procedures and compositions described above can be made without departing from the spirit or scope of the present invention, as set forth in the following claims.

CLAIMS

What is claimed is:

1. A method of treating herpes infection, the method comprising:

administering an antiviral therapy to a subject receiving a vaccine formulation, so that efficacy of the vaccine formulation and/or the antiviral therapy is improved in the subject over a specified time period relative to a subject receiving only the vaccine formulation or the antiviral therapy;

wherein the vaccine formulation comprises an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain, and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide; and

wherein the efficacy of the vaccine formulation and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, increased time to first herpes recurrence, increased time to next herpes recurrence, decreased genital herpes lesion rate, decreased genital herpes lesion frequency, decreased genital herpes lesion duration, decreased rate of genital herpes outbreaks, decreased duration of genital herpes outbreaks, decreased anogenital HSV shedding rate, decreased anogenital HSV shedding magnitude, decreased or no increase of valacyclovir dose, decrease of one or more herpes signs or symptoms or increased health-related quality of life.

2. The method of claim 1, further comprising administering the antiviral therapy to a population of subjects receiving a vaccine formulation.

3. The method of claim 2, wherein the efficacy of the vaccine formulation and/or the antiviral therapy is improved in the population over a specified time period relative to subjects receiving only the vaccine formulation or the antiviral therapy.

4. The method of claim 3, wherein the efficacy of the vaccine formulation and/or the antiviral therapy is measured or indicated by one or more of increasing a proportion of subjects

who are genital herpes recurrence-free, increasing time to first herpes recurrence, increasing time to next herpes recurrence, decreasing genital herpes lesion rate, decreasing genital herpes lesion frequency, decreasing genital herpes lesion duration, decreasing rate of genital herpes outbreaks, decreasing duration of genital herpes outbreaks, decreasing anogenital HSV shedding rate, decreasing anogenital HSV shedding magnitude, decreased or no increase of valacyclovir dose, decreasing one or more herpes signs or symptoms, or increasing health-related quality of life.

5. A method of treating herpes infection, the method comprising:

administering an antiviral therapy to a population receiving a vaccine formulation, so that efficacy of the vaccine formulation and/or the antiviral therapy is improved in the population over a specified time period relative to subjects receiving only the vaccine formulation or the antiviral therapy;

wherein the vaccine formulation comprises an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain, and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide; and

wherein the efficacy of the vaccine formulation and/or the antiviral therapy is measured or indicated by one or more of increasing a proportion of subjects who are genital herpes recurrence-free, increasing time to first herpes recurrence, increasing time to next herpes recurrence, decreasing genital herpes lesion rate, decreasing genital herpes lesion frequency, decreasing genital herpes lesion duration, decreasing rate of genital herpes outbreaks, decreasing duration of genital herpes outbreaks, decreasing anogenital HSV shedding rate, decreasing anogenital HSV shedding magnitude, decreased or no increase of valacyclovir dose, decreasing one or more herpes signs or symptoms or increasing health-related quality of life.

6. A method of treating herpes infection, the method comprising:

administering a vaccine formulation to a subject receiving antiviral therapy, so that efficacy of the vaccine formulation and/or antiviral therapy is improved in the subject over a

specified time period relative to a subject receiving only the vaccine formulation or the antiviral therapy;

wherein the vaccine formulation comprises an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide; and

wherein the efficacy of the vaccine formulation and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, increased time to first herpes recurrence, increased time to next herpes recurrence, decreased genital herpes lesion rate, decreased genital herpes lesion frequency, decreased genital herpes lesion duration, decreased rate of genital herpes outbreaks, decreased duration of genital herpes outbreaks, decreased anogenital HSV shedding rate, decreased anogenital HSV shedding magnitude, decreased or no increase of valacyclovir dose, decrease of one or more herpes signs or symptoms or increased health-related quality of life.

7. The method of claim 6, further comprising administering the vaccine therapy to a population of subjects receiving an antiviral therapy.

8. The method of claim 7, wherein the efficacy of the vaccine formulation and/or the antiviral therapy is improved in the population over a specified time period relative to subjects receiving only the vaccine formulation or the antiviral therapy.

9. The method of claim 8, wherein the efficacy of the vaccine formulation and/or the antiviral therapy is measured or indicated by one or more of increasing a proportion of subjects who are genital herpes recurrence-free, increasing time to first herpes recurrence, increasing time to next herpes recurrence, decreasing genital herpes lesion rate, decreasing genital herpes lesion frequency, decreasing genital herpes lesion duration, decreasing rate of genital herpes outbreaks, decreasing duration of genital herpes outbreaks, decreasing anogenital HSV shedding rate,

decreasing anogenital HSVshedding magnitude, decreased or no increase of valacyclovir dose, decreasing one or more herpes signs or symptoms or increasing health-related quality of life.

10. A method of treating herpes infection, the method comprising:

administering a vaccine formulation to a population of subjects receiving antiviral therapy, so that efficacy of the vaccine formulation and/or the antiviral therapy is improved in the population over a specified time period relative to subjects receiving only the vaccine formulation or the antiviral therapy;

wherein the vaccine formulation comprises an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide; and

wherein the efficacy of the vaccine formulation and/or the antiviral therapy is measured or indicated by one or more of increasing a proportion of subjects who are genital herpes recurrence-free, increasing time to first herpes recurrence, increasing time to next herpes recurrence, decreasing genital herpes lesion rate, decreasing genital herpes lesion frequency, decreasing genital herpes lesion duration, decreasing rate of genital herpes outbreaks, decreasing duration of genital herpes outbreaks, decreasing anogenital HSV shedding rate, decreasing anogenital HSV- shedding magnitude, decreased or no increase of valacyclovir dose, decreasing one or more herpes signs or symptoms or increasing health-related quality of life.

11. A method of treating herpes infection, the method comprising:

administering to a subject a therapy to achieve an increase in efficacy

wherein the increase in efficacy of the therapy is measured or indicated by one or more of increasing a proportion of subjects who are genital herpes recurrence-free, increasing time to first herpes recurrence, increasing time to next herpes recurrence, decreasing genital herpes lesion rate, decreasing genital herpes lesion frequency, decreasing genital herpes lesion duration, decreasing rate of genital herpes outbreaks, decreasing duration of genital herpes outbreaks, decreasing anogenital HSV shedding rate, decreasing anogenital HSV shedding magnitude,

decreased or no increase of valacyclovir dose, decreasing one or more herpes signs or symptoms or increasing health-related quality of life; and

wherein the therapy comprises administration of one or both of (i) a vaccine formulation comprising an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide, and (ii) an antiviral therapy, so that the subject receives both.

12. The method of claim 11, wherein the therapy comprises administration of the vaccine formulation to a subject receiving antiviral therapy.

13. The method of claim 1211 wherein the therapy comprises administration of antiviral therapy to a subject receiving the vaccine formulation.

14. A method of treating herpes infection, the method comprising:

administering a vaccine formulation to a subject receiving antiviral therapy, so that efficacy of the antiviral therapy is improved in the subject over a specified time period relative to a subject receiving only the antiviral therapy;

wherein the vaccine formulation comprises an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide; and

wherein the efficacy of the antiviral therapy is measured or indicated by one or more of: decreased time to lesion healing, decreased time to cessation of pain, decreased time to cessation of viral shedding, decreased herpes recurrence rate and decreased rate of symptomatic acquisition of herpes in susceptible partners.

15. The method of claim 15, further comprising administering the vaccine formulation to a population of subjects receiving an antiviral therapy.

16. The method of claim 15, wherein the efficacy of the antiviral therapy is improved in the population over a specified time period relative to subjects receiving only the antiviral therapy.

17. The method of claim 16, wherein the efficacy of the antiviral therapy is measured or indicated by one or more of increasing a proportion of subjects who are genital herpes recurrence-free, decreasing time to lesion healing, decreasing time to cessation of pain, decreasing time to cessation of viral shedding, decreasing herpes recurrent rate and decreasing rate of symptomatic acquisition of herpes in susceptible partners.

18. A method of treating herpes infection, the method comprising:

administering a vaccine formulation to a population of subjects receiving antiviral therapy, so that efficacy of the antiviral therapy is improved in the population over a specified time period relative to subjects receiving only the antiviral therapy;

wherein the vaccine formulation comprises an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide; and

wherein the increase in efficacy of the antiviral therapy is measured or indicated by one or more of increasing a proportion of subjects who are genital herpes recurrence-free, decreasing time to lesion healing, decreasing time to cessation of pain, decreasing time to cessation of viral shedding, decreasing herpes recurrent rate and decreasing rate of symptomatic acquisition of herpes in susceptible partners.

19. A method of treating herpes infection, the method comprising:

administering to a subject (i) an antiviral therapy, and (ii) a vaccine formulation comprising an HSV-2 gD2 polypeptide, wherein the gD2 polypeptide has an internal deletion of all or part of the transmembrane domain and an HSV-2 ICP4 polypeptide or an immunogenic fragment comprising at least 8 contiguous amino acids of HSV-2 ICP4 polypeptide,

so that efficacy of the vaccine formulation and/or the antiviral therapy is improved in the subject over a specified time period relative to a subject receiving only the vaccine formulation or the antiviral therapy;

wherein the efficacy of the vaccine formulation and/or the antiviral therapy is measured or indicated by one or more of: a genital herpes recurrence-free period, increased time to first herpes recurrence, increased time to next herpes recurrence, decreased genital herpes lesion rate, decreased genital herpes lesion frequency, decreased genital herpes lesion duration, decreased rate of genital herpes outbreaks, decreased duration of genital herpes outbreaks, decreased anogenital HSV shedding rate, decreased anogenital HSV shedding magnitude, decreased or no increase of valacyclovir dose, a decrease of one or more herpes signs or symptoms or increased health-related quality of life.

20. The method of any one of the preceding claims, wherein the antiviral therapy is selected from the group consisting of famciclovir, valacyclovir, acyclovir and combinations thereof.

21. The method of claim 20, wherein the antiviral therapy is valacyclovir.

22. The method of claim 20, wherein the subjects receive about 500 mg to about 1 g of antiviral therapy per dose.

23. The method of any one of the preceding claims, wherein the efficacy of the vaccine formulation and/or antiviral therapy is assessed at, at least 3 months, 6 months, 12 months, 18 months, 24 months, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years after administration of therapy.

24. The method of any one of the preceding claims, wherein the efficacy of the vaccine formulation and/or the efficacy of the antiviral therapy is assessed at least 6 months after administration of therapy.

25. The method of any one of the preceding claims, wherein the health related quality of life is measured by the EuroQoL-5 Domains-5 Levels (EQ-5D-5L) questionnaire.

26. The method of claim 25, wherein the subject completes the EQ-5D-5L questionnaire when not experiencing a genital herpes outbreak and or/on about each day of an outbreak.

27. The method of any one of the preceding claims, wherein the decrease in one or more herpes signs or symptoms is a decrease in the percentage of days with herpes-related signs or symptoms and/or a decrease in the magnitude of herpes-related signs or symptoms.

28. The method of any one of the preceding claims, wherein viral shedding is measured is by real-time quantitative polymerase chain reaction (PCR).

29. The method of any one of the preceding claims, wherein the efficacy of the vaccine formulation is measured or indicated by an increase in humoral response and/or an increase in cellular response.

30. The method of claim 29, wherein the increase in humoral response is measured or indicated by an increase in magnitude of response or fold rise from baseline of HSV-2 immunoglobulin G (IgG) levels and/or of HSV-2 neutralizing antibody levels.

31. The method of claim 30, wherein the increase in humoral response is indicated by a 4-fold or greater rise in IgG titer from baseline.

32. The method of claim 30, wherein the increase in humoral response is indicated by a 2-fold or greater rise in 50% neutralizing antibody titer from baseline.

33. The method of claim 29, wherein the cellular response is an increase in secretion of granzyme B (GrB) levels.

34. The method of claim 33, wherein the increase in cellular response is measured or indicated by an increase in magnitude of response or fold rise from baseline of granzyme B (GrB) levels.

35. The method of claim 29, wherein the cellular response is an increase in IFNγ secretion for T cells.

36. The method of any one of the preceding claims, wherein the population of subjects: are not receiving therapy comprising tenofovir, lysine, a supplement or medication, other than valacyclovir, e.g., a therapy known to or purported to affect herpes outbreak frequency or intensity; do not have a history of ocular herpes infection, herpes-related erythema multiforme, herpes meningitis or herpes encephalitis; do not have active genital HSV-2 lesions; are not immunocompromised; are not receiving systemic immunosuppressive medication; do not have an autoimmune disease; have not previously had an autoimmune disease; do not have HIV, hepatitis B or hepatitis C; do not have history of hypersensitivity to any component of the vaccine formulation; do not have a clinically significant laboratory abnormality except for (i) creatinine kinase in subjects with an identified exercise regimen and hepatic and renal enzyme levels within normal limits or (ii) isolated Grade 2 unconjugated bilirubin in fasting subjects with a history of Gilbert's syndrome; have not received any other vaccine containing an HSV-2 antigen; have not received an investigational product within 30 days prior to the first dose of the vaccine formulation; have not received a blood product within 90 days prior to the first dose of the vaccine formulation; have not received a live vaccine within 28 days prior to the first dose of the vaccine formulation; have not received any other vaccine within 14 days prior to the first dose of the vaccine formulation; do not receive any other vaccine from the first dose until 28 days after the third dose; are not pregnant or nursing; or any combination thereof.

37. The method of any one of the preceding claims, wherein the population of subjects: are male, female or non-pregnant female; are at least 18 years old and less than 51 years old, are at

least 10, 11, 12, 13, 14, 15, 16 or 17 years old, are 51 years or older; are receiving antiviral therapy; have a history of at least one genital herpes outbreak while on antiviral therapy within 6 months of treatment; have a history of greater than 5 outbreaks of genital herpes within one year if not receiving antiviral therapy; have been diagnosed with genital herpes infection for greater than 1 year; use contraception for 28 days before and 90 days after treatment with the vaccine formulation; or any combination thereof.

38. The method of claim 37, wherein receiving antiviral therapy includes receiving valacyclovir therapy at a dose of 500 mg or 1 g once a day for 14 days prior to first dose of the vaccine formulation.

39. The method of claim 37, wherein the diagnosis of genital herpes infection comprises Western blot analysis for one or more HSV-2 antigens; PCR (e.g., type-specific PCR); viral culture (e.g., type-specific viral culture); or compatible clinical history and positive HerpeSelect® 2 enzyme-linked immunosorbent assay IgG with an index value >3.5 or a positive LIAISON® HSV-2 Type Specific IgG.

40. The method of any one of the preceding claims, wherein the vaccine formulation and antiviral therapy are administered concurrently or sequentially.

41. The method of any one of the preceding claims, wherein the vaccine formulation comprises an HSV-2 gD2 polypeptide comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, or 99% identity to SEQ ID NO:4, and an HSV-2 ICP4 polypeptide comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, or 99% identity to SEQ ID NO:2.

42. The method of any one of the preceding claims, wherein the vaccine formulation comprises an adjuvant.

43. The method of claim 42, wherein the adjuvant is one or more purified fractions of *Quillaja saponins*.

44. The method of claim 43, wherein the adjuvant comprises saponin fraction A and saponin fraction C.

45. The vaccine formulation of claim 42, wherein the adjuvant further comprises cholesterol and phosphatidyl choline.

46. The vaccine formulation of claim 42, wherein the adjuvant is in the form of particles.

47. The vaccine formulation of claim 46, 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.

48. The vaccine formulation of claim 42, wherein the adjuvant is Matrix-M2.

49. The vaccine formulation of claim 42, wherein the adjuvant is present in an amount of about 50 µg.

50. The method of any one of the preceding claims, wherein the subjects receive suppressive antiviral therapy.

51. The method of claim 50, wherein the subjects are administered antiviral therapy once a day.

52. The method of claim 50, wherein the antiviral therapy is administered orally.

53. The method of any one of the preceding claims, wherein the vaccine formulation is administered intramuscularly.

54. The method of any one of the preceding claims, wherein the vaccine formulation is administered in at least one dose, at least two doses, at least three doses, at least four doses, at least 5 doses or more.

55. The method of any one of the preceding claims, wherein the vaccine formulation is administered at intervals of about 7 days, 14 days, 21 days, 28 days, 35 days, 42 days, 49 days, 56 days or longer.

56. The method of 54, wherein the total dose is about 0.5 mL to about 1.0 mL.

57. The method of any one of the preceding claims, wherein upon administration to a subject, the vaccine formulation treats infection by HSV-1, HSV-2, or HSV-1 and HSV-2 in the subject.

58. The method of any one of the preceding claims, wherein the herpes is genital herpes.

59. The method of any one of the preceding claims, wherein the vaccine formulation comprises about 10 μg, 20 μg, 30 μg, 60 μg, or 100 μg of each of the gD2 polypeptide and the ICP4 polypeptide and/or about 25 μg, 50 μg or 75 μg of adjuvant.

60. The method of claim 59, wherein the vaccine formulation comprises about 60 μg of the gD2 polypeptide, about 60 μg of the ICP4 polypeptide and about 50 μg of adjuvant.

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Clinical Abnormalities

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Local Reaction to Injectable Product				
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Vital Signs				
Fever (°C) (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	>40 >104
Tachycardia - beats per minute	101 – 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mmHg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mmHg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

Figure 1A

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Systemic (General)				
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 gms/24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Systemic Illness				
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Figure 1B

Tables for Laboratory Abnormalities

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Serum				
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23-26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

Figure 1C

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Hematology				
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)
Urine				
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

Figure 1D

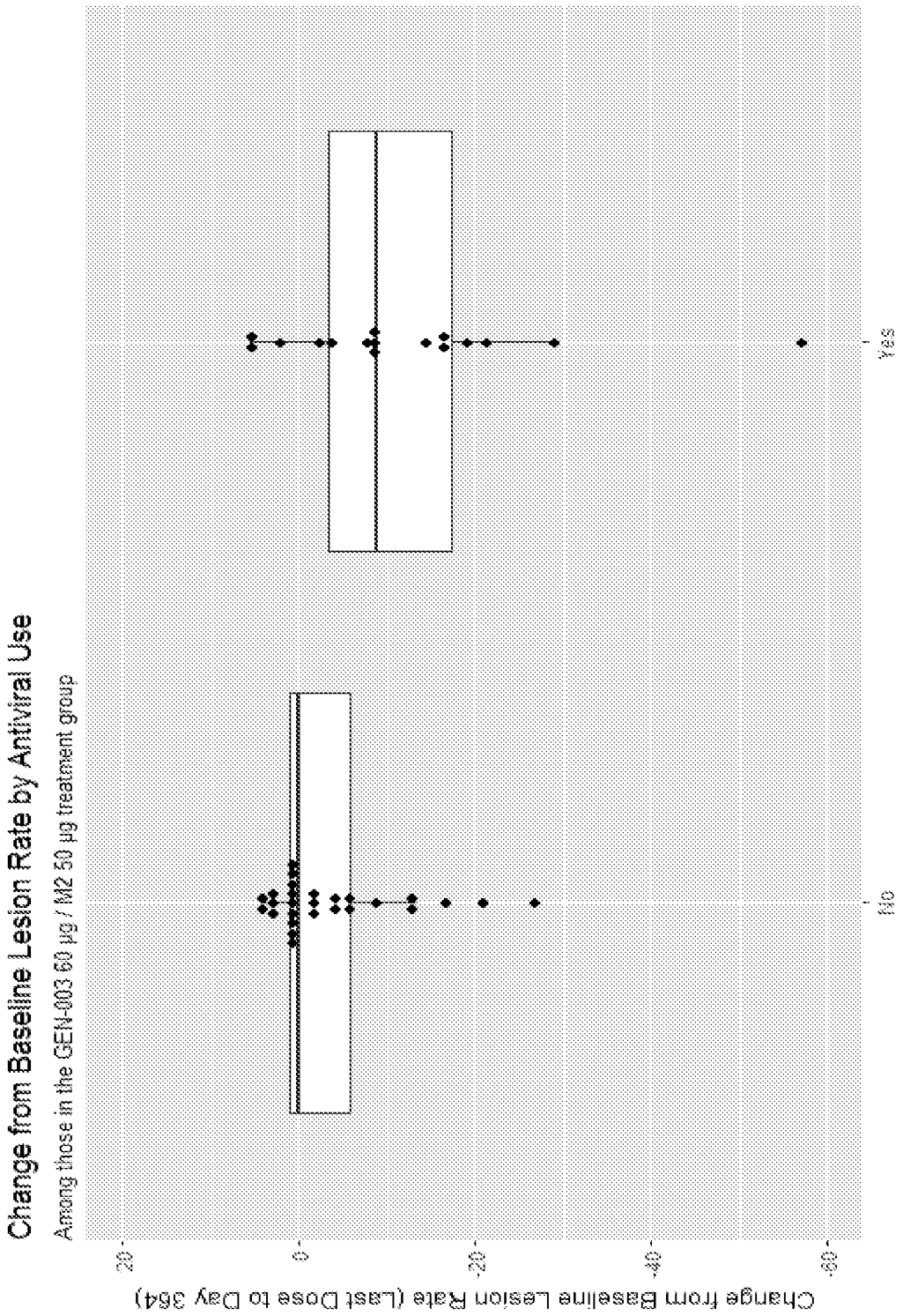
Change from Baseline Lesion Rate by Antiviral Use
Among those in the GEN-003 60 µg / M2 50 µg treatment group
Change from Baseline Lesion Rate (Last Dose to Day 364)
20
0
-20
-40
-60
No
Yes
Antiviral Use

FIGURE 2

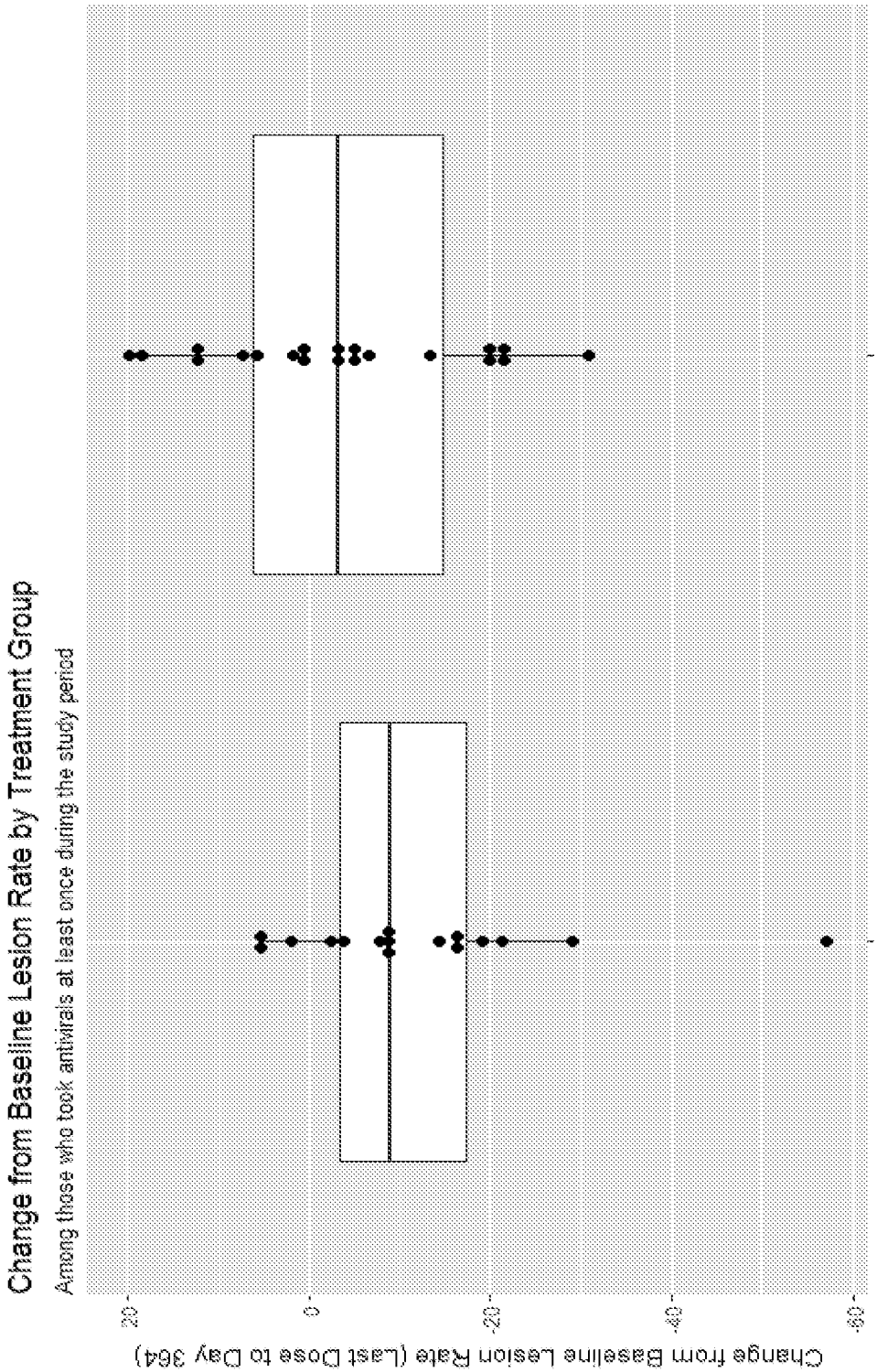
Change from Baseline Lesion Rate by Treatment Group
Among those who took antivirals at least once during the study period
Change from Baseline Lesion Rate (Last Dose to Day 364)
20
0
-20
-40
-60
GEN-003 60 µg / M2 60 µg
Placebo
Treatment Group

FIGURE 3

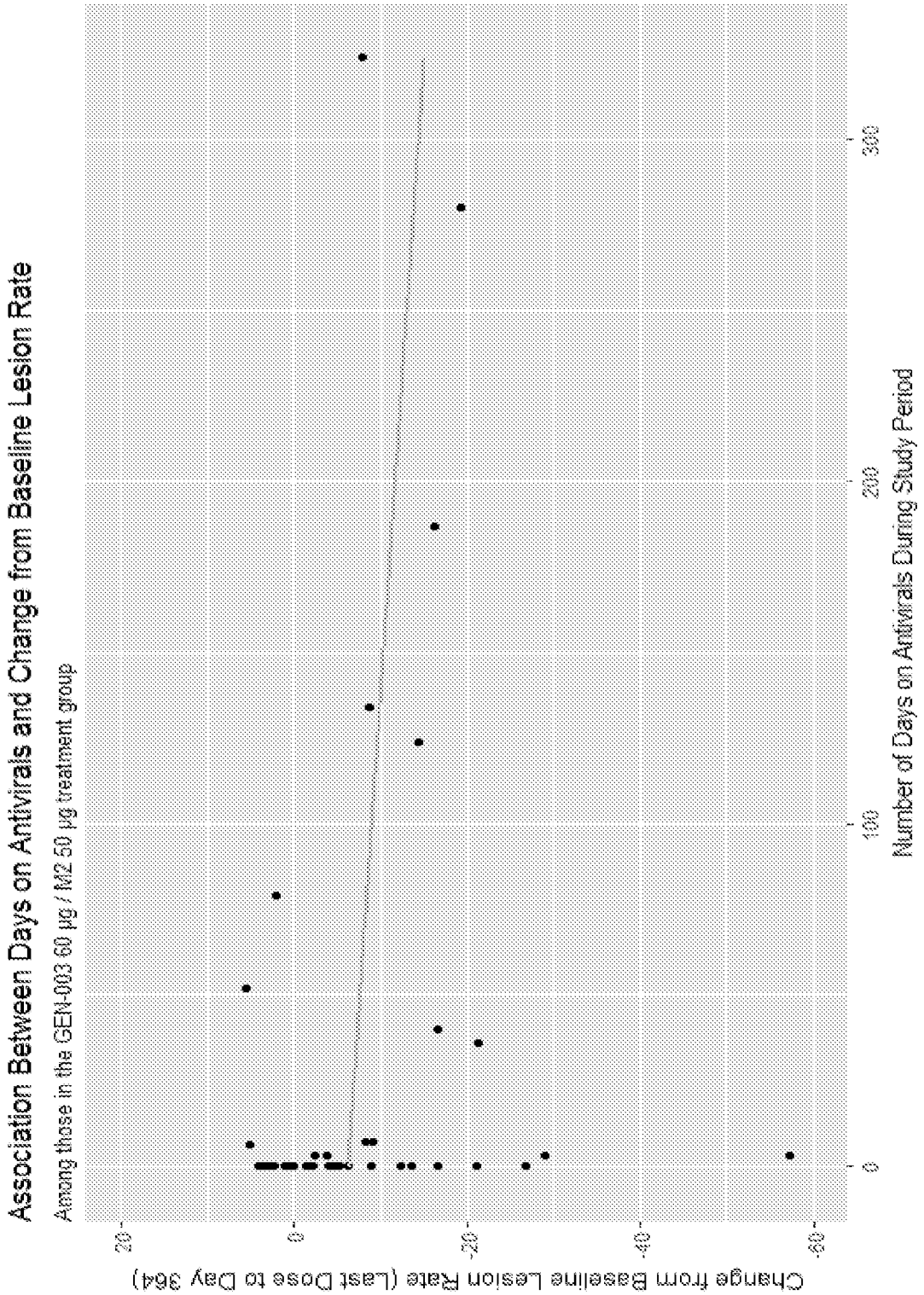
Association Between Days on Antivirals and Change from Baseline Lesion Rate
Among those in the GEN-003 60 µg / M2 50 µg treatment group
Change from Baseline Lesion Rate (Last Dose to Day 364)
20
0
-20
-40
-60
0
100
200
300
Number of Days on Antivirals During Study Period

FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53835

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 14/035; G01N 33/569; A61K 38/00, 39/245; C12N 7/04 (2017.01)

CPC - C07K 14/005, 14/035; G01N 33/56994; A61K 38/00, 39/245

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 8,617,564 B2 (LONG, D et al). 31 December 2013; column 1, line 44, column 3, lines 38, 39, 44, 50, column 30, lines 50, 52, 53, column 23, lines 2, 40, 47, 50, 55, 61, 62 claim 1, 2, 7, 27.	11-13, 20/11-13, 21/20/11-13 ---------- 1-10, 14-19, 20/1-10, 20/14-19, 21/20/1-10, 21/20/14-19, 22/20/1-19
Y	(THERMET, A et al.) DNA vaccination in combination or not with lamivudine treatment breaks humoral immune tolerance and enhances cccDNA clearance in the duck model of chronic hepatitis B virus infection. The Journal of General Virology. 1 May 2008, Vol. 89, Pt. 5; pages 1192-1201; abstract; DOI: 10.1099/vir.0.83583-0	1-10, 14-19, 20/1-10, 20/14-19, 21/20/1-10, 21/20/14-19, 22/20/1-19
Y	(KIMBERLIN, DW et al.) Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Cambridge: Cambridge University Press, 2007 [retrieved on 16 November 2017]. Retrieved from the Internet: <URL: https://www.ncbi.nlm.nih.gov/books/NBK47376/>; Chapter 64, page 8, paragraph 6; page 10, paragraph 7; ISBN-13: 978-0-521-82714-0.	22/20/1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2017 (21.11.2017)	05 DEC 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53835

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53835

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 23-60
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.